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Unraveling neural and behavioral mechanisms of cognitive self-attenuation and alienation

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ABSTRACT

The present thesis aimed at investigating behavioral and neural underpinnings of the mechanisms related to the different aspects of self-monitoring. The first aim was to study functional connectivity alterations related to the mechanisms accounting for the alienation in psychotic patients and those at high-risk to develop it. The second aim was to extend the fundamental knowledge of whether higher-level cognitive processes beyond sensorimotor involvement are subject to attenuation and whether it is affected in psychotic patients with thought insertion.

In Part I of the thesis, I have studied whether the neural mechanisms (PH-network) accounting for the presence hallucination (PH), the experience that someone is here when no one is around, could also be relevant to understand alienation experienced in psychotic patients. In Study 1, I have investigated psychotic patients with passivity experiences where ones' actions, thoughts and emotions are perceived as not self-generated and caused by an external entity. In Study 2, individuals with 22q11 deletion syndrome who are at high-risk for psychosis development were investigated. In both populations, reduced functional connectivity between fronto-temporal connections within the PH-network was revealed. Taken together, these studies show that PH-network is affected not only when psychosis manifests but also in individuals prone to develop psychosis. The current findings strengthen the relevance of PH mechanisms to explain the occurrence of psychotic symptoms, specifically the alienation, and potentially could provide a biomarker for the disease development.

In Part II of the thesis, I have investigated self-attenuation, an important aspect for the sense of agency, during the cognitive function of numerosity estimations in healthy individuals and psychotic patients with thought insertion. In Study 3, a novel fMRI task was designed, allowing a controlled comparison of numerosity estimations for self and externally generated words in healthy volunteers. For the first time, self-attenuation during cognitive function beyond sensorimotor processing was reported. It was linked to the functional network involving intraparietal sulcus (key numerosity region) and extended areas more generally associated with attenuation processes. This work was continued in Study 4, where psychotic patients with thought insertion were studied. I showed that cognitive self-attenuation during

numerosity estimations can be observed in patients with thought insertion and is related to altered executive functioning. Importantly, an increased functional connectivity within network related to attenuation processing during numerosity estimations was found in patients with thought insertion suggesting insufficient attenuation at the neural level. Lastly, I found the association between the altered functional connectivity within the PH-network and cognitive self-attenuation, providing a link between two different aspects related to the self-monitoring in patients with thought insertion.

To summarize, I present new insights into the different mechanisms related to self-monitoring, which would help to understand the manifestation of psychotic symptoms and develop prevention strategies.

Keywords: brain imaging, functional MRI, psychosis, psychotic symptoms, attenuation, cognition, numerosity, schizophrenia, presence hallucination, presence hallucination network, disconnection

RESUME

La présente thèse visait à étudier les fondements comportementaux et neuronaux des mécanismes liés aux différents aspects de l'autosurveillance. Le premier objectif était d'étudier les altérations de la connectivité fonctionnelle liées aux mécanismes responsables de l'aliénation chez les patients psychotiques et ceux à haut risque de la développer. Le second objectif était d'étendre les connaissances fondamentales pour savoir si les processus cognitifs de haut niveau au-delà de l'implication sensorimotrice sont sujets à une atténuation et si celle-ci est affectée chez les patients psychotiques avec insertion de la pensée.

Dans la première partie de la thèse, j'ai étudié si les mécanismes neuronaux (réseau PH) expliquant l'hallucination de présence (PH), l'expérience que quelqu'un est là quand il n'y a personne autour, pourraient également être pertinents pour comprendre l'aliénation vécue chez les patients psychotiques. Dans l'étude 1, j'ai étudié des patients psychotiques ayant des expériences de passivité où les actions, les pensées et les émotions de chacun sont perçues comme non auto-générées et causées par une entité externe. Dans l'étude 2, j'ai étudié des personnes atteintes du syndrome de délétion 22q11 qui sont à haut risque de développer une psychose. Dans les deux populations, une connectivité fonctionnelle réduite entre les connexions fronto-temporelles au sein du réseau PH a été révélée. Prises ensemble, ces études montrent que le réseau PH est affecté non seulement lorsque la psychose se manifeste, mais aussi chez les individus susceptibles de développer une psychose. Les résultats actuels renforcent la pertinence des mécanismes du PH pour expliquer l'apparition de symptômes psychotiques, en particulier l'aliénation, et pourraient potentiellement fournir un biomarqueur pour le développement de la maladie.

Dans la deuxième partie de la thèse, j'ai étudié l'auto-attention, un aspect important pour le sens de l'agence, pendant la fonction cognitive des estimations de la numération chez les individus en bonne santé et les patients psychotiques avec insertion de pensées. Dans l'étude 3, une nouvelle tâche d'IRMf a été conçue, permettant une comparaison contrôlée des estimations de la numérotation pour les mots générés par soi-même et par l'extérieur chez des volontaires sains. Pour la première fois, une auto-atténuation de la fonction cognitive au-delà du traitement sensorimoteur a été signalée. Elle était liée au réseau fonctionnel

impliquant le sillon intrapariétal (région clé de la numération) et des zones étendues plus généralement associées aux processus d'atténuation. Ces travaux ont été poursuivis dans l'étude 4, où des patients psychotiques avec insertion de pensées ont été étudiés. J'ai montré que l'auto-atténuation cognitive pendant les estimations de la numérologie peut être observée chez les patients avec insertion de la pensée et est liée à une altération du fonctionnement exécutif. Il est important de noter qu'une connectivité fonctionnelle accrue au sein du réseau, liée au traitement de l'atténuation pendant les estimations de la numération, a été trouvée chez les patients souffrant d'insertion de pensées, ce qui suggère une atténuation insuffisante au niveau neural.

Pour résumer, je présente de nouvelles perspectives sur les différents mécanismes liés à l'auto-surveillance, qui permettraient de comprendre la manifestation des symptômes psychotiques et de développer des stratégies de prévention.

Mots clés: imagerie cérébrale, IRM fonctionnelle, psychose, symptômes psychotiques, atténuation, cognition, numération, schizophrénie, hallucination de présence, réseau d'hallucination de présence, déconnexion

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ABBREVIATIONS

22q11DS - 22q11.2 microdeletion syndrome

BOLD – Blood oxygen level dependant

CI(95%) – confidence interval range

DLB – Dementia with Lewy Bodies

EPI – Echo planar imaging

FD – Framewise displacement

FDR – False discovery rate

fMRI – Functional magnetic resonance imaging

FWE – Family wise error

FWHM – full-width half-maximum

IFG – Inferior frontal gyrus

IPL – Inferior parietal lobule

IPS – Intraparietal sulcus

LoA – Loss of agency

MNI – Montreal Neurological Institute space

MPRAGE – Magnetization-prepared rapid acquisition with gradient echo

PANSS – Positive and negative symptom scale

PD – Parkinson's disease

PE – Passivity experiences

PET – Positron emission tomography

PH – Presence hallucination

pMTG – Posterior middle temporal gyrus

riPH – robot-induce presence hallucination

ROI – Region of interest

rs – Resting state

SD – Standard deviation

SMA - Supplementary motor area

TI – Thought insertion

vPMC – Ventral premotor cortex

GENERAL INTRODUCTION

"The mind commands the body and it obeys. The mind orders itself and meets resistance."

— Frank Herbert, Dune

1.1 MOTIVATION

Have you ever wondered how you know when actions, thoughts and emotions are generated by yourself and not someone else? What brain mechanism underlies this attribution? Or even more strikingly, what are the consequences if this distinction between self and other blurs? These are some of the questions that have stirred the neuroscience field for decades. The great amount of research on this topic is dedicated to exploring what processes are involved in this self-other distinction by studying healthy individuals and the ones in whom this boundary has become unclear. Yet, a lot of questions still remain to be answered. For example, what brain mechanisms are affected in individuals who misinterpret their own thoughts being produced by someone else or hear non-existent voices? Is our brain processing internal cognitive information differently when it is triggered by ourselves or externally? During my thesis I have investigated these questions by performing various experiments and looking at different clinical populations, which I will introduce and describe in the following sections.

The human ability to distinguish self- versus externally-generated stimuli is crucial for a coherent self-representation and orientation in the environment. In certain mental states such as psychosis, the perception of reality is blurred where self-monitoring affecting self-other distinction is disturbed. One of the leading theoretical frameworks accounting for self-monitoring is the internal forward model (Farrer and Frith, 2002; Miall and Wolpert, 1996). It postulates that the sensory effects of actions are compared with internal sensory predictions. When sensory predictions match the actual sensory feedback, actions are perceived as self-generated and their sensory consequences are attenuated (Wolpert and Flanagan, 2001). Importantly, altered sensory prediction mechanisms of self-generated actions accounting for coherent self-monitoring (Frith, 2005; Shergill et al., 2005) have been associated with psychotic passivity experiences characterized by patients failing to correctly self-attribute

their own motor actions, perceptions, thoughts or emotions (Graham-Schmidt et al., 2018). Passivity experiences could be accounted for by two fundamentally distinct aspects related to self-monitoring: a positive aspect accounting for alienation (experience of an alien entity) and a negative aspect accounting for a loss of self-attribution. It has been suggested that decreased fronto-temporal functional connectivity is linked to altered sensory predictions and that this could account for self-other discrimination disturbances such as passivity and loss of self-agency (negative aspect), which is in line with the disconnection hypothesis for hallucinations (Friston, 1998; Stephan et al., 2009). Yet, this is not sufficient to explain positive aspects of psychosis such as the experience of the presence of an alien entity (e.g., presence hallucination) or being under the influence of such an entity (e.g., patients experiencing the thoughts of someone else in their mind). For example, the lack of thought agency (negative aspect) is not sufficient to account for thought insertion characterized by the experience that certain thoughts, occurring in one's mind, are not one's own thoughts but of somebody else (Martin and Pacherie, 2013; Sousa and Swiney, 2013), because they also include the conscious encounter that the thoughts are caused by another alien person (positive aspect) (Schneider, 1959; Taylor, 1972; Koehler, 1979; Mullins and Spence, 2014). The positive element is therefore essential, considering that the lack of self-attribution (in thought awareness) also occurs in healthy subjects as is the case of unbidden thoughts (Gallagher, 2004; Martin and Pacherie, 2013), but the positive aspect observed during the thought insertion does not. A similar phenomenological dichotomy applies to auditory verbal hallucinations (e.g., loss of self-attribution of the heard voice, hearing another person's voice) and other passivity experiences.

In the first part of my thesis (Part I) I have focused on a specific psychotic symptom called presence hallucination (PH), which recently has been induced experimentally and linked to deficits in bodily self-monitoring (Blanke et al., 2014). Mechanisms related to PH could potentially account for alienation (positive aspect of passivity experiences) (Blanke et al., 2014, Salomon et al., 2020). PH has been defined as a false perception that someone is nearby when no one is actually present and can occur in neurological (e.g., epilepsy, Parkinson's disease) and psychiatric patients (e.g., schizophrenia). Our lab has investigated the sensorimotor mechanisms of PH as well as the neural correlates associated with this hallucination in neurological patients and in healthy participants and determined the key brain areas defining the PH-network (see Annexes: Bernasconi et al., 2020). It is proposed that

brain mechanisms involved in PH, and hence the experience of the presence of an alien agent, could also account for the positive aspects related to alienation in patients with a broader spectrum of psychotic symptoms including more particularly, passivity experiences (Blanke et al., 2014; Salomon et al., 2020). However, up to date there are no studies investigating the altered PH neural mechanisms in psychotic patients. Showing the link between the brain areas associated with PH and psychotic symptoms such as passivity experiences could partly unravel the mechanistic underpinnings of these symptoms, especially accounting for the alienation (positive aspect). Therefore, in Studies 1 and 4 of the thesis I have investigated whether functional connectivity of the PH-network is affected and related to passivity experiences, where self-monitoring of patient's actions, perceptions, or thoughts is disturbed and being perceived to be caused by an external entity.

An important aspect as mentioned above for self-other distinction is an attenuation of self-generated stimuli that is considered to be a consequence of prediction mechanisms helping to distinguish self-versus externally generated signals and play a role in a sense of agency (Blakemore et al., 1998). Indeed, previous studies have shown that self-produced overt stimuli in auditory (Timm et al., 2014), visual (Hughes and Waszak, 2011) and somatosensory domains (Shergill et al., 2013) are attenuated compared to externally generated ones, both at the perceptual and neural level. Covert stimuli such as motor imagery (Kilteni et al., 2018) and inner speech (Jack et al., 2019) are shown to be attenuated as well. Notably, the attenuation of self-generated stimuli is shown to be reduced in psychotic patients (Ford et al., 2014; Shergill et al., 2005) and is suggested to account for the negative aspect of psychotic experiences (such as loss of agency). Yet, it is not known whether self-attenuation extends to inner cognitive processes beyond sensorimotor systems involvement (cognitive self-attenuation). Understanding behavioral and neural mechanisms of cognitive self-attenuation could help to unravel the alterations causing passivity experiences such as thought insertion. Thus, in the second part of my thesis (Part II), I have investigated behavioral and neural mechanisms related to self-attenuation and studied whether attenuation also occurs during the higher-level cognitive function of numerosity estimations in healthy participants and how such cognitive self-attenuation is affected in psychotic patients.

1.2 OVERVIEW

Part I of my thesis focusses on the functional connectivity within the PH-network (see Annexes: Bernasconi et al., 2020) in different clinical populations: psychotic patients with passivity experiences (Study 1) and in non-psychotic individuals with 22q11 deletion syndrome (Study 2) which represent a population with high prevalence of developing psychosis. In Study 1 (Stripeikyte et al., *submitted*), I have observed decreased fronto-temporal functional connectivity within the PH-network in psychotic patients with passivity experiences as compared to psychotic patients without such symptoms. I showed reduced fronto-temporal functional connectivity within the PH-network and extended areas involved in auditory processing (e.g., auditory verbal hallucinations are the most common passivity experience), in patients with passivity experiences as compared to those without. These results provide further evidence for a link between the PH-network and auditory verbal hallucinations and corroborates earlier behavioral observations where sensorimotor discrepancies inducing the PH lead to auditory-verbal misperceptions, specifically in psychotic patients (Salomon et al., 2020). In Study 2 (Blondiaux, Potheegadoo, Stripeikyte et al., *in preparation*), the PH-network was further investigated in non-psychotic individuals with 22q11 deletion syndrome, which represent one of the highest genetic risk factors for developing schizophrenia (30%) (Schneider et al., 2014). This provided us with a unique model to study behavioral and neural markers for psychosis by investigating the PH-network's functional connectivity as it could be an early sign for psychosis and predict the disease development. The data showed a reduction in functional connectivity within the PH-network mostly involving fronto-temporal connections in individuals with 22q11 deletion syndrome as compared to healthy age-matched controls. This finding stands in line with the functional disconnection observed in psychotic patients (Study 1). Both studies corroborate the disconnection hypothesis for hallucinations (Friston, 1998; Stephan et al., 2009) as fronto-temporal disconnections were observed. We conclude that PH-network is affected not only when psychosis manifests but also in individuals prone to develop psychosis, strengthening the relevance of PH mechanisms to explain the occurrence of psychotic symptoms, specifically the positive aspect related to the alienation. Potentially, PH and associated neural mechanisms could provide a biomarker for the psychosis development.

In the Part II of my thesis, I have investigated the behavioral and neural mechanisms of cognitive self-attenuation in healthy volunteers and psychotic patients with thought insertion. In Study 3 (Stripeikyte et al., *in preparation*) we have designed a novel fMRI task where we looked at numerosity estimations for actively versus passively generated words in healthy volunteers. The study reports evidence for self-attenuation in cognition. Cognitive self-attenuation was reflected in stronger underestimation for the number of self-generated words compared to externally generated words. Further, we revealed that a key brain region of numerical processing (intraparietal sulcus region, IPS) is functionally related to the extended network usually reported to be involved in attenuation processes more generally. This functional network could provide a signal for behavioral attenuation during numerosity estimations. Study 3 for the first time shows that self-attenuation can be observed for cognitive function of numerosity estimations and is related to cognitive brain region (IPS). In another project of my thesis (Study 4; Stripeikyte et al., *in preparation*), I continued to investigate self-attenuation in cognition. This study focused on psychotic patients who suffer from the clinical symptom of thought insertion. We investigated behavioral cognitive self-attenuation which could account for the negative aspect of the symptom (loss of thought agency). Further, we were interested to relate behavioral findings to the PH-network functional connectivity as it accounts to the positive aspect of alienation (e.g., someone else put thoughts in one's mind). First, we compared numerosity estimations for actively and passively generated words between psychotic patients with and without thought insertion (and healthy controls) and further investigated associations between task performance and frontal executive function. Although cognitive self-attenuation was found in patients as well as in control groups, I discovered that only psychotic patients with the clinical symptom of thought insertion, but not patients without such symptoms, showed a significant correlation between the levels of cognitive self-attenuation and frontal executive function. Second, I observed reduced PH-network connectivity in fronto-temporal regions in psychotic patients with thought insertion compared to without (as in Study 1). The main finding consisted of increased connectivity between the left frontal areas in psychotic patients with thought insertion compared to without (and healthy controls). Crucially, this increased connectivity between the left frontal areas negatively correlated with cognitive self-attenuation. Here, we have shown that cognitive self-attenuation accounting for the negative aspect of thought insertion (loss of thought agency) is associated with altered PH-network connectivity, the mechanism related to the positive aspect of alienation. This brings us to a better

understanding of this complex symptom providing an evidence that two different mechanisms related to the self-monitoring are involved.

Taken together, these experiments give a more comprehensive insight into the behavioural and neural mechanisms of passivity experiences in psychotic patients and the related mechanisms in healthy humans, by approaching these phenomena from several different angles related to self-monitoring. In Part I of my thesis, I have investigated a network related to a bodily self-monitoring deficit, namely involved in the occurrence of PH and revealed systematic fronto-temporal disconnections within the PH-network in psychotic patients with passivity experiences and individuals at high-risk for psychosis. We suggest that PH-network alterations could account partly for the occurrence of psychotic symptoms and these neuroscientific insights could be used to improve diagnostics and prognostics of psychotic patients. In Part II, I developed a new behavioral paradigm and investigated whether the previously described self-attenuation for sensory processes, which is important for perceptual self-other distinction, extends to higher-level cognitive processes such as numerosity estimations. I have shown behaviorally that self-attenuation is present during numerosity estimations and is reflected in the network involving IPS, a key numerosity region, and areas often reported in attenuation processes. Next to deficits in sensory perception, deficits related to cognitive self-attenuation could account for the negative aspect of psychotic symptoms (loss of agency), for example in the case of thought insertion which is also shown to be linked to the altered mechanisms accounting for alienation.

1.3 BACKGROUND

The background part of the thesis will provide the basic concepts needed for the better understanding of the studies presented in the Part I and Part II.

1.3.1 Neuroimaging

Over the last decades, functional Magnetic Resonance Imaging (fMRI) has become one of the most used non-invasive neuroimaging techniques to study functional organization of the human brain. fMRI measures local hemodynamic changes in the brain, known as Blood-Oxygen-Level-Dependent signal (BOLD) that indirectly reflect neuronal activity (Viallon et al., 2015). The great advantage of fMRI is the possibility to obtain a three dimensional and a large coverage of images of the brain over time and relatively good spatial resolution enabling to study the contributions of distant brain areas. This technique has been widely used to study brain activity in healthy and clinical populations (Glover, 2011; Whitten, 2012). There are several types of possible fMRI acquisition techniques like resting-state or task fMRI which were used in this thesis work. First technique is resting-state fMRI where participants do not perform any specific task but are cognitively alert while the brain images are acquired (Study 1, 2 and 4). Resting-state fMRI is very useful to study clinical populations with cognitive disabilities as it does not require to attend the task (Biswal, 2012). The classical analysis of resting-state fMRI data informs about the static functional connectivity, that is a temporal correlation over the scanning duration between the seeds and the rest of the brain or between regions of interest (ROIs), which could form a network (Biswal et al., 1995). The other technique used in Study 3 is task-based fMRI where participants are performing certain task while acquiring fMRI data. This allows to identify brain regions that activate or de-activate in response to the task by preforming statistical comparisons between the BOLD activity during the different task conditions (Friston et al., 1995).

1.3.2 Model accounting for self-monitoring

Another important concept in this thesis is self-monitoring that accounts for self-other distinction. Self-monitoring based on sensorimotor predictions is a crucial aspect of normal cognitive and sensorimotor functioning and allows online updating of actions and prediction of sensory consequences related to self-generated stimuli (Miall and Wolpert, 1996). It is

considered that the sense of agency, which is described as a feeling of being the agent of one's own actions and thoughts is important for self-monitoring as it enables to distinguish between self and externally produced stimuli (Gallagher, 2000; Jeannerod, 2003).

One of the influential accounts explaining self-monitoring is based on the internal forward model (Figure 1.1) where motor and other related signal commands are used to predict the sensory consequences of one's own action. If these predictive signals match the current sensory input, movements are perceived as self-generated. However, if there is a difference between the prediction and the actual sensory feedback, the action is considered as externally produced (Blakemore et al., 1998). On the neural and behavioral level, it has been shown that if the prediction and actual sensory outcome match, the signal is attenuated (Blakemore et al., 2000; Blakemore et al., 1998; Shergill et al., 2013, 2005; Weiskrantz et al., 1971). For example, if we attempt to reach a dot in space, the predictive signal about the possible action outcome is sent at the same time as a motor command to reach it. If we reach the dot as was expected, we attribute this action to ourselves but if it does not match to what was predicted we attribute the action to external agent. More about the attenuation processes extending not only to the perceptual but also to the cognitive domain are investigated in the Part II of the thesis.

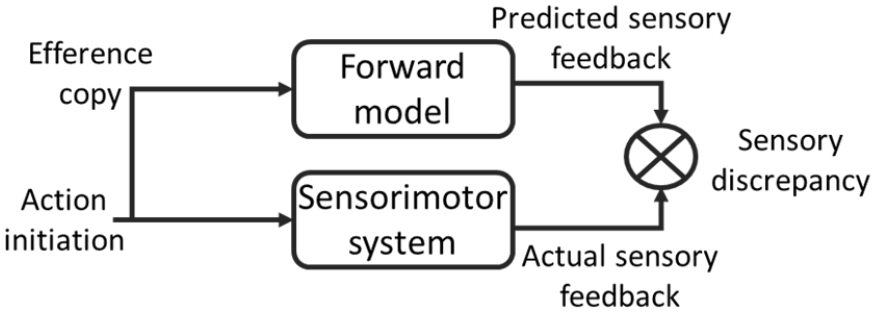

Figure 1.1: Internal forward model scheme based on Blakemore, et al., 2000. The input motor command is used to make prediction about the sensory consequence of the action. The prediction is based on the efferent copy of the motor command. If the actual and predicted sensory feedbacks are matching, then the movement is considered as self-generated. However, if there is a discrepancy, an action is attributed to an external agent.

1.3.3 Psychosis

The focus of my thesis was to study the mechanisms related to the different aspects of self-monitoring. Clinical populations (e.g., patients with schizophrenia or neurodegenerative disorders) with psychosis where self-monitoring is shown to be affected offers an invaluable opportunity to better understand related deficits which in turn would help to prevent and predict disease outcomes. Generally, psychosis describes the conditions that affect one's mind where thoughts and perceptions are disturbed and contact with reality is blurred. Psychotic symptoms manifest of delusions (false beliefs) and hallucinations (seeing or hearing things that others cannot).

Passivity experiences

A group of psychotic symptoms such as somatic passivity, thought withdrawal, thought insertion, delusions of control, or auditory verbal hallucinations are termed passivity experiences (PE; see table 1.1) and formerly known as schneiderian first-rank symptoms (Schneider, 1959). These symptoms share common features described by two phenomenologically distinct aspects related to self-monitoring. A negative aspect where disturbed self-other perception occurs by misattributing self-generated thoughts, emotions and actions (loss of agency) and a positive aspect where they are attributed to an external alien entity (alienation).

Symptoms and phenomenology (Mellor, 1970)	Examples of patients' reports
1. Audible thoughts Patient experiences voices (own or others) speaking his/her thoughts aloud, like an echo.	«I thought I must put the kettle on, then less than a second after, I heard the voice saying ' I must put the kettle on'».
2. Voices arguing Two or more voices arguing; they can be in disagreement or discussing about the patient (as a 3rd person).	1st voice: «I knew he (the patient) would not be able to do it, his mother told him so». 2nd voice: «He would be just fine».
3. Voices commenting one's actions Voices (heard as internal or external) comment on patient's actions/activities as they occur.	Voice: «He is now opening his bag… he cannot find his keys».
4. Thought insertion Thoughts coming from external agent are imposed to patients' mind.	«My mind is not mine for a few seconds… minutes…My mind is a vessel where god puts his thoughts. He will crush us all…».
5. Thought withdrawal Own thoughts are being taken away from patients' mind by an external force.	«I was thinking of my daughter's graduation…. and suddenly my thoughts are sucked out of my mind … like by a pump, then it's empty …».
6. Made volitional acts Actions completely under the control of an external agent. Patient is a passive observer of his own actions.	«I'm a puppet manipulated by cosmic strings. When the strings are pulled, my body moves and I cannot prevent it».
7. Influence played on body (somatic passivity) Bodily sensations imposed upon patients by an external agent without them being able to do anything about it. The sensations are genuine.	«X-rays entering my body and burning my skin and organs».
8. Thought broadcast (or diffusion) Thoughts escape from patients' mind, fly away and can be experienced by others.	«My thoughts leave my head on a type of mental ticker-tape. Everyone around has only to pass the tape through their mind and they know my thoughts».
9. Made feelings Patients experience emotions and feelings that are not his own but coming from an external agent.	«I cannot help laughing (having giggles)… It makes me angry and ashamed about that. It can happen anywhere, in the tram, …».
10. Made impulses Strong impulse overcomes the patient to which he gives away. The impulse and consequent action is not felt as his own.	«I don't want to do it, but I must, this feeling kills me». E.g., putting on fire, scarifications.
11. Delusional perception A normal sensory perception is given a specific meaning by the patients - delusional interpretation.	«I saw footsteps on the snow and I knew I should be aware … I knew immediately I have to go to the bank and take all my money, capitalism will ruin us.»

Table 1.1: The list of passivity experiences and examples of the patient's reports on how they perceive them. The list is based on the Mellor, 1970. Some examples are taken from the internal patient interviews with the authorization of Dr. Jevita Potheegadoo.

Schizophrenia

One of the clinical populations in which psychosis is often observed is schizophrenia patients and the occurrence of psychotic symptoms are suggestive of schizophrenia diagnosis (Taylor, 1972). About one percent of the world population suffer from schizophrenia. Schizophrenia is a debilitating, chronic mental illness, which is described by auditory and visual hallucinations, delusions and chaotic speech and behavior. In order to diagnose schizophrenia the symptoms must be present for at least six months (American Psychiatric Association, 2000). Individuals who at the beginning of the disease are medicated once and experience psychotic symptoms once or several times are first ascribed as first-episode psychotic patients, where later with the intensified occurrence of symptom manifestation and treatment can be diagnosed with schizophrenia. Environmental and genetic factors have been shown to play a role in the development of the disease. There is an increased probability to develop the disorder if someone in the family has it and heritability rates vary between 60 to 85% (Dacquino et al., 2015; Lichtenstein et al., 2009). Besides, environmental features such as substance abuse, prenatal stress, childhood or brain traumas, and bad living conditions influence disease development (Walsh and Yun, 2013). Usually the onset of the disease is around mid-twenties, but it also can become apparent at a younger age during puberty. Schizophrenic and first-episode psychotic patients with psychosis were investigated in Study 1 and 4 to better understand the neural and behavioral mechanisms accounting for psychotic experiences.

22q11 deletion syndrome

Another clinical population with 22q11 deletion syndrome which is a neurodevelopmental disorder caused by chromosomal microdeletion of 1.5 to 3 million base pairs on chromosome 22 band q11.2 provides an interesting human model to study schizophrenia and psychosis (McDonald-McGinn et al., 2015; Murphy et al., 1999). 22q11 deletion syndrome is approximately occurring in one over 4000 births and is defined by a complex somatic, cognitive and neuropsychological phenotype (Biswas and Furniss, 2016). Around a quarter of individuals with this syndrome would develop schizophrenia, and around 30% of them are having the onset of the disease before the age of eighteen years old (Bassett & Chow, 1999; Murphy et al., 1999; Schneider et al., 2014). Psychosis in individuals with 22q11 deletion syndrome has been described to progress as a continuum with an increasing severity of

psychotic symptoms where hallucinations manifests before delusions (Schneider et al., 2014). In Study 2, behavioral and neural mechanisms related to self-monitoring were investigated in individuals with 22q11 deletion syndrome and how it could be related to the psychosis development.

Neurodegenerative disorders

Psychosis with psychotic symptoms occur in patients with neurodegenerative disorders like Parkinson's disease (PD) or dementia with Lewy bodies (DLB). Classically, PD is associated with motor symptoms such as tremor, rigidity, bradykinesia. Yet, non-motor traits are present in PD as including psychotic symptoms, which can occur and increase in severity over the different stages of the disease (Fénelon and Alves, 2010; Ravina et al., 2007). It is suggested that early manifestation of psychotic symptoms in PD is related to a higher negative outcome over the course of the disease (Aarsland et al., 2000; Ffytche et al., 2017; Frisina et al., 2008; Ravina et al., 2007). Among the psychotic symptoms, there are so called, minor hallucinations which include visual illusions, passage hallucinations (e.g., sensation that someone or an animal is passing in the peripheral visual filed) and presence hallucinations (discussed in more detail in below chapter) (Pagonabarraga et al., 2016). Interestingly, minor hallucinations could occur before the onset of motor symptoms (Pagonabarraga et al., 2016), offering a great potential to study as prognostic and diagnostic features for the disorder. Another neurodegenerative disorder, where psychosis and psychotic symptoms are often occurring is DLB (Nagahama et al., 2010; Tzeng et al., 2018). Patients with DLB suffer from progressive cognitive decline that disrupt normal social and occupational functions and up to 85% of patients are shown to manifest with spontaneous parkinsonian features (McKeith et al., 2017).

1.3.4 Mechanisms of psychotic symptoms

Discrepancies of the self-monitoring in psychotic patients

Recent theories in the literature state that psychotic symptoms are partly caused by errors in self-monitoring (ability to distinguish self-generated actions or thoughts from externally generated ones) (Blakemore et al., 2000; Frith, 2012; Frith et al., 2000). The model used to explain the errors in self-monitoring is an internal forward model (see above for more details) (Blakemore et al., 2000; Fletcher and Frith, 2009; Friston and Frith, 1995; Frith, 2005, 1992;

Graham-Schmidt et al., 2018; Pynn and DeSouza, 2013; Schneider, 1959). Indeed, the model explains psychotic symptoms such as auditory verbal hallucinations or passivity sensations well and have been supported by a large number of clinical studies (Cho and Wu, 2013; Martin et al., 2016; Shergill et al., 2013). For example, it has been showed that psychotic patients with auditory verbal hallucinations do not attenuate electrophysiological signal when they are the ones who generate the sound, while healthy subjects attenuate the signal for self-generated sound (Ford et al., 2014). In the Part II, Study 4 of the thesis, the attenuation processes in higher-level cognitive domain are investigated in psychotic patients with thought insertion.

Disconnection hypothesis

On the neural level, it has been proposed that psychosis and hallucinations are accounted by a reduced functional connectivity (correlation or coherence among measures of neurophysiological signal between different brain areas) and described as the disconnection hypothesis (Friston, 1998; Hahamy et al., 2014; Karbasforoushan and Woodward, 2013; Skudlarski et al., 2010). Numerous studies have reported reduction in functional connectivity in schizophrenia patients (González-Vivas et al., 2019; Karbasforoushan and Woodward, 2013; Mwansisya et al., 2017; Satterthwaite and Baker, 2015). Particularly, fronto-temporal disconnectivity is considered to be involved in the occurrence of psychotic symptoms as it is suggested that the prediction signals are altered due to disconnectivity and therefore psychotic patients misattribute self-generated signal with an external agent (Friston et al., 2016; Chris D. Frith et al., 2000; Lawrie et al., 2002).

1.3.5 Presence hallucination

Psychotic symptoms, specifically, passivity experiences are described as experiencing an external entity (e.g. hearing someone else's voice: auditory verbal hallucination, positive aspect). A fascinating phenomenon where someone else is felt in close proximity when actually no one is around, is called presence hallucination (PH) (Brugger et al., 1996; Critchley, 1955, 1950; Fénelon et al., 2000; Jaspers, 1913; Lhermitte, 1939) and is suggested that its mechanisms could account more generally for the alienation in psychotic patients (Blanke et al., 2014, Salomon et al., 2020). PH was first described by a psychiatrist Karl Jaspers in early 20th century: "*patients who have a certain feeling (in the mental sense) or awareness that someone is close by, behind them or above them, someone that they can in no way perceive*

with the external senses, yet whose actual/concrete presence is clearly experienced" (Jaspers, 1913). It has been reported to occur in psychiatric disorders like schizophrenia (Jaspers, 1913) or neurological disorders like epilepsy (e.g., Ardila & Gómez, 1988; Blanke et al., 2003; Brugger et al., 1996; Critchley, 1950, 1955), Parkinson's disease (Fénelon et al., 2000; Llorca et al., 2016; Williams et al., 2008; Wood et al., 2015), Dementia with Lewy bodies (Nagahama et al., 2010; Nicastro et al., 2018), even in patients with focal brain lesions (Blanke et al., 2014, 2008, 2003; Brugger, 1994; Brugger et al., 1996). Surprisingly, PH has also been reported in healthy individuals during extreme conditions when performing monotonous repetitive movements (Brugger et al., 1999; Bychowski, 1943; Nightingale, 1982; Rohde et al., 2014; Suedfeld and Mocellin, 1987). Reported prevalence of PH in schizophrenia and PD patients reaches more than 40% (Fénelon and Alves, 2010; Llorca et al., 2016). Yet, it is very rarely systematically investigated in clinical practices probably due to the reluctance of patients to talk about it and the difficulty to diagnose and classify such hallucinations (Holroyd et al., 2001; Ravina et al., 2007).

PH is suggested to be related to altered own body perception (Arzy et al., 2006; Blanke et al., 2014, 2003; Brugger et al., 1996; Critchley, 1955; Engerth and Hoff, 1929; Jaspers, 1913) and disturbed processing of sensorimotor signals (Blanke et al., 2014, Bernasconi et al., 2020, Salomon et al., 2020). The proposition that PH is a disorder of own body perception is compatible with a prominent account for hallucinations in psychosis positing that passivity experiences may be associated with faulty sensorimotor prediction mechanisms (Fletcher and Frith, 2009; Frith, 1992).

Experimental induction of PH

PH have been studied under laboratory controlled conditions in healthy (Blanke et al., 2014; Orepic et al., 2020) and psychotic patients (Salomon et al., 2020). The technology is based on a robotic system (Figure 1.2) which is able to generate spatial-temporal sensorimotor discrepancies (Blanke et al., 2014). In more detail, individuals are asked to perform a repeated poking movement with the index finger of the right hand using a robotic system placed in front of them. The movement performed by the participant is recorded and then electronically transmitted to a back robot providing tactile feedback to the participants' back. The tactile feedback can either by synchronous with 0ms delay or asynchronous with 500ms delay between the performed movement and the touch received on the back. The

asynchronous condition has been associated with the induction of the PH (Blanke et al., 2014). In addition to PH, participants during the asynchronous condition usually report experiencing passivity sensations (Blanke et al., 2014; Orepic et al., 2020; Salomon et al., 2020). Further, the induction of PH has also been linked to auditory misattribution, relating PH and passivity experiences observed in psychotic patients (Orepic et al., 2020; Salomon et al., 2020).

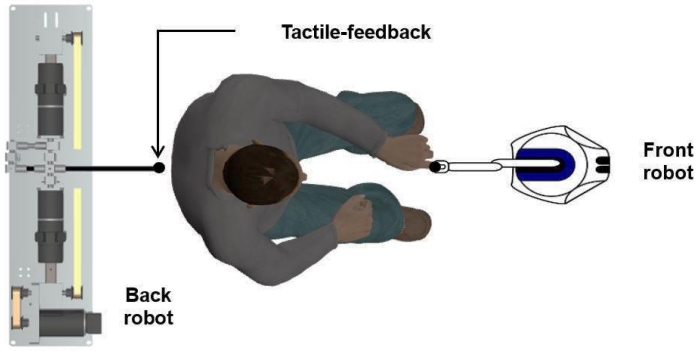

Figure 1.2: A depiction of the robotic device setup designed to induce presence hallucination (PH) in a safe and controlled manner. Individuals would perform a repetitive poking like movement with the index finger by manipulating the front robot. The performed movement would be translated to a back robot that could provide a tactile feedback to the individuals back in a synchronous (no time delay) or asynchronous (500 ms delay) mode. Figure adapted from Blanke et al., 2014.

Neural underpinnings of PH

As mentioned above, PH has been reported in individuals with focal brain lesions, particularly in the parietal, temporal and occipital areas (Brugger et al., 1996; Critchley, 1979; Hécaen and Ajuriaguerra, 1952), or epileptic patient where it was showed that stimulating temporo-parietal cortex triggers PH (Arzy et al., 2006). These findings were extended by investigating the common brain areas in patients with lesions and symptomatic PH. The temporo-parietal cortex, insula and fronto-parietal cortex were found as the most overlapping areas in these patients (Blanke et al., 2014). More recently, neural origins of PH have been studied, in our laboratory, in healthy subjects combining fMRI and MR-compatible robotics (Hara et al., 2014) and lesion network mapping (Boes et al., 2015) using lesions of neurological patients with symptomatic PH (see Annexes: Bernasconi et al., 2020). This led to the definition of a PH-network, consisting of the inferior frontal gyrus, posterior middle temporal gyrus, and ventral

premotor cortex in right and left hemispheres. The relevance of PH and its related neural mechanisms for psychotic patients are investigated in Study 1, 2 and 4.

1.3.6 Numerosity

In this thesis I employed numerosity estimations (Part II of the thesis) as a tool to assess higher-level cognitive processes and to test whether it is a subject to self-attenuation important for self-monitoring and self-other distinction.

Numerosity estimations, defined as approximate judgments when counting is not involved (Dehaene, 1997) are one of the most studied higher-level cognitive processes over the last 30 years. The properties of numerosity has been thoroughly investigated in visual and auditory domains (see the reviews: Burr et al. 2018; Anobile et al. 2016). Among the extensive amount of traits of numerosity estimations, a few should be specifically mentioned as they are relevant for this thesis. First, numerosity is defined as an abstract innate property, which does not require learning and is independent of the sensory attributes and their physical parameters (Burr et al., 2018; Nieder, 2018; Piazza et al., 2006). For example, we are able to approximately report the number of figures which are presented in different size, shape and color. We can discriminate number of items independent whether it is presented as a flash of dots or played sounds in a row. Of course, the precision of such numerosity estimations vary depending on the features of the presented items, yet we are still able to report the approximate numerosity. Interestingly, numerosity perception has been observed in various animal groups such as monkeys, dogs and fish (for the review see Nieder, 2018). It has been shown that even baby's have the ability to distinguish different numerosities (Dehaene, 1997). Further it is important to mention, that numerosity perception follows different regimes (Anobile et al., 2016) (Figure 1.3). The estimation of usually up to four items is errorless and is called subitizing range. The higher numerosities are estimated with the rapid but linearly increasing error prone behavior following Weber's law (Piazza et al., 2004). A great example to illustrate Weber's law, is a comparison of weights; if we need to compare between 10 and 15 grams or between 550 and 555 grams, we would be better at distinguishing weights in the former comparison, as the difference between two weights is a bigger fraction of the original weight compared to latter example of weights. Very high numerosities, which include dense and overlapping items are processed following texture-based mechanisms. There, small linear

changes are usually not noticed, and density of items is determined by following square root of numerosity.

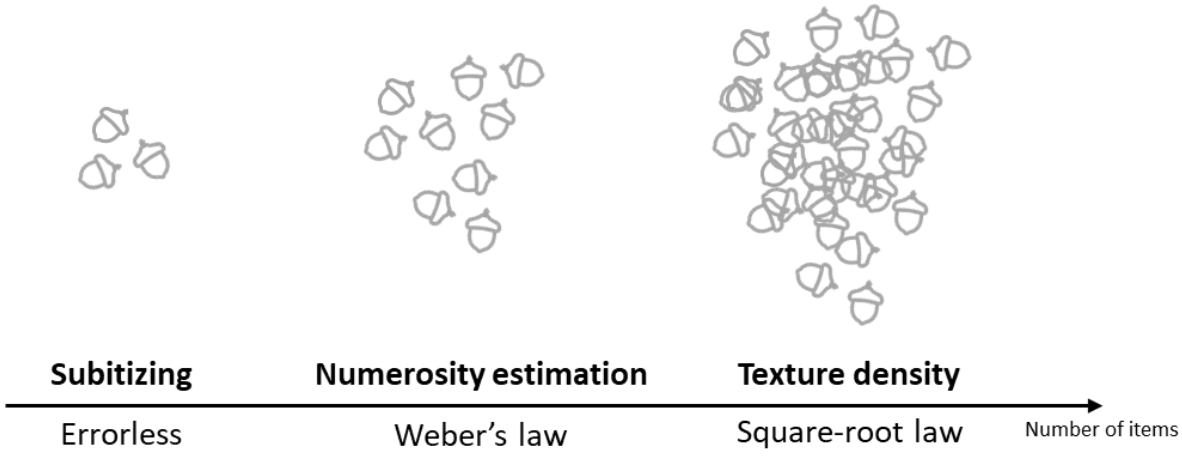

Figure 1.3: Regimes for numerosity perception. Three key regimes are represented: subitizing, numerosity estimation and texture density. Designed based on Anobile et al., 2016.

The role of intraparietal sulcus (IPS) as a key area in numerosity processing has been established over extensive imaging studies in humans and primates (for review see Arsalidou & Taylor, 2011). Thus, well defined traits of numerosity estimations offers a possibility to investigate more complex relationships such as how it differentiates between self-generated internal actions like words produced during inner speech and externally generated words (Part II of the thesis).

PART I

Understanding neural mechanisms related to hallucinations in psychotic patients could provide an immense possibility for further treatment and prevention. Recent efforts in the scientific field have shed light about the neural mechanisms of the fascinating phenomenon: presence hallucination. The mechanistic understanding of the presence hallucination offers a possibility to investigate a broader spectrum of psychotic symptoms called passivity experiences. The key trait of various passivity experiences are the misattribution of self-generated actions, thoughts or emotions to an external entity. It is suggested that the mechanisms accounting for the experience of an external entity during the passivity experiences and presence hallucination could be shared. The Part I of the thesis is dedicated to understand whether the neural mechanisms accounting for the presence hallucination are of relevance and altered in psychotic patients with passivity experiences (Study 1) or even in individuals who are at high-risk to develop psychotic symptoms (Study 2). These two studies revealed that indeed functional connectivity is affected in the network accounting for the occurrence of PH. Specifically, observed reduction in functional connectivity stands in line with the disconnection hypothesis for hallucinations. Further, Study 1 shows that alterations in the PH-network are also extended to other areas usually reported to be affected in psychotic patients with auditory verbal hallucinations. This suggest that mechanisms accounting for the external entity and domain specific alterations of hallucinations (e.g., auditory areas) are affected and related. Study 2 has revealed that yet not psychotic individuals with 22q11 deletion syndrome but with high risk of developing it already have reduced functional connectivity compared to healthy age matched controls in a similar areas as psychotic patients with passivity experiences.

2.1 STUDY 1: FRONTO-TEMPORAL DISCONNECTION WITHIN THE PRESENCE HALLUCINATION NETWORK IN PSYCHOTIC PATIENTS WITH PASSIVITY EXPERIENCES

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GS, NF, GR, OB developed the study concept and contributed to the study design. Patients' recruitment, testing and data collection were performed by JP, PP, KD, PC, PH. GS performed the data analysis. GS, JP, and OB drafted the paper; all authors provided critical revisions and approved the final version of the article for submission. The authors are grateful for all patients for their participation and clinical staff for data collection and patients recruitment.

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Disclosure statement

The authors report no conflict of interest.

2.1.1 Abstract

Psychosis, characterized by hallucinations and delusions, is a common feature of psychiatric disease, especially schizophrenia. One prominent theory posits that psychosis is driven by abnormal sensorimotor predictions leading to the misattribution of self-related events. This misattribution has been linked to passivity experiences (PE), such as loss of agency and, more recently, to presence hallucinations (PH), defined as the conscious experience of the presence of an alien agent while no person is actually present. PH has been observed in schizophrenia, Parkinson's disease, and neurological patients with brain lesions and, recently, the brain mechanisms of PH (PH-network) have been determined comprising bilateral posterior middle temporal gyrus (pMTG), inferior frontal gyrus (IFG), and ventral premotor cortex (vPMC). Given that the experience of an alien agent is a common feature of PE, we here analyzed the functional connectivity within the PH-network in psychotic patients with (N=39) versus without PE (N=26). We observed reduced fronto-temporal functional connectivity in patients with PE compared to patients without PE between the right pMTG and the right and left IFG of the PH-network. Moreover, when seeding from these altered regions, we observed specific alterations with brain regions commonly linked to auditory verbal hallucinations (such as Heschl's gyrus). The present connectivity findings within the PH-network extend the disconnection hypothesis for hallucinations to the specific case of PH and associates the PH-network with key brain regions for frequent psychotic symptoms such as auditory verbal hallucinations, showing that PH are relevant to the study of the brain mechanisms of psychosis and PE.

Keywords: psychosis, hallucinations, functional connectivity, disconnection, presence hallucination network, resting-state fMRI

2.1.2 Introduction

Psychosis is an abnormal mental state including hallucinations and delusions that is frequent in psychiatric conditions such as schizophrenia (1) and may include abnormal sensations such as somatic passivity, thought withdrawal, thought insertion, delusions of control, or auditory verbal hallucinations. Such psychotic symptoms, formerly known as Schneiderian first-rank symptoms (2,3), have been termed passivity experiences (PE) (4), arguably reflecting a failure to self-attribute one's perceptions, thoughts, actions, or emotions (5,6). Related clinical research further suggested that PE and psychosis may be associated with impairments in self-monitoring (5–8), an essential aspect of sensorimotor functioning, based on sensorimotor and predictive mechanisms (i.e., prediction of sensory consequences related to self-generated actions) (9–11). Disturbances in self-monitoring have been argued to reflect a diminished demarcation of the self-other boundary and often consist of at least two phenomenally distinct aspects. A negative aspect is characterized by a loss in subjective experience, such as a loss of self-attribution (i.e., sense of agency or ownership); a positive aspect is characterized by the appearance of foreign or alien elements in subjective experience. Thought insertion, for example, is characterized by the experience that certain thoughts, occurring in one's mind, are not one's own thoughts (negative aspect; loss of thought agency or thought ownership) (12,13). However, the lack of thought agency is not sufficient to account for thought insertion, because patients with thought insertion not only experience that their thoughts are not their own, but those of another alien person (positive aspect) (14–17). The additional positive element is therefore also important, because lack of self-attribution (in thought awareness) also occurs in healthy subjects (as is the case of unbidden thoughts (13,18)), whereas the positive aspect of thought insertion does not. A similar phenomenological dichotomy applies to auditory verbal hallucinations and other PE.

The large majority of previous neuroscience research of psychosis has targeted the first, negative element of PE, characterized by lack or decreases of self-attribution (19–22), with very few studies on the second positive element of PE (4,23). Here we sought to target the second, positive, aspect of PE. Based on recent findings including behavioral, clinical, and imaging work (4,24–26) it has been suggested that a particular complex symptom, presence hallucination (PH), and the associated neural system may be of relevance for psychosis, and especially the positive element of PE. PH is frequently observed in patients with schizophrenia

(27) and is defined as the vivid sensation that another alien person is nearby when no one is actually present and can neither be seen or heard. PH has recently been linked to the disturbances in self-monitoring and sensorimotor processing (4,24,25) related to bodily self-consciousness (24,28,29).

Although PH occurs in around 50% of patients with schizophrenia, it is often overlooked in psychiatric patients (27) and it is accordingly not known how PH relates to PE in psychotic patients. However, PH is very frequent in patients with neurodegenerative disease suffering from hallucinations such as Parkinson's disease (25,30) and dementia with Lewy bodies (31,32). PH has also been studied in neurological patients suffering from focal brain damage (30,33,34). Importantly, it has also been demonstrated that PH and somatic passivity, mental states that phenomenologically resemble PE, can be experimentally induced in healthy participants (24). This controlled induction of a mild PE-like mental state was induced by robotically-controlled sensorimotor stimulation, showing that PH are caused by the misperception of the source and the identity of sensorimotor signals of one's own body. The cortical network of neurological and robot-induced PH have been investigated recently by Bernasconi, Blondiaux et al. (25) using lesion network mapping (35) and MRI-compatible robotics (36). This led to the definition of a PH-network, consisting of bilateral inferior frontal gyrus, posterior middle temporal gyrus, and ventral premotor cortex that was impaired in Parkinson's disease patients with symptomatic PH (25). However, it is currently unknown whether the PH-network is impaired in psychotic patients with PE.

In the present study, we studied whether functional connectivity in the PH-network differed between a group of psychotic patients with symptomatic PE versus a group of psychotic patients without PE, allowing us to distinguish possible symptom-specific neural activities from disease-related effects. Based on the disconnection hypothesis in schizophrenia (37–40) we hypothesized, first, to observe decreased functional connectivity within the PH-network, especially of fronto-temporal connections, based on previous findings linking impaired sensorimotor integration in schizophrenia (41–43). Second, using the whole-brain analysis we investigated whether the affected PH-network areas would be characterized by abnormal functional connectivity, especially with areas previously shown to be involved in PE.

2.1.3 Methods

Participants

Sixty-five psychotic patients were included in this study. Part of the patients (N=23) was recruited from the outpatient clinic of the department of psychiatry, Lausanne University Hospitals, Switzerland, and met DSM-IV criteria for schizophrenia or schizoaffective disorder (44). Another part of the patients (N=42), who met threshold criteria for psychosis, as defined by the 'Psychosis threshold' subscale of the Comprehensive Assessment of At-Risk Mental States, were recruited from the TIPP Program (Treatment and Early Intervention in Psychosis Program, University Hospital, Lausanne, Switzerland) (45). Neurological disorders and severe head trauma were exclusion criteria for all patients. Informed written consent in accordance with institutional guidelines (protocol approved by the Cantonal Ethics Commission of Vaud, Switzerland) was obtained for all subjects.

Patients underwent an in-depth clinical assessment by a trained psychiatrist where the frequency and severity of symptoms were evaluated. Symptom severity was assessed in the patient groups using the Positive and Negative Syndrome Scale (PANSS) (46). Lifetime occurrence of passivity experiences (PE; auditory verbal hallucinations; somatic passivity; thought broadcasting; thought insertion; thought withdrawal) inspired by the Scale for the Assessment of Positive Symptoms (SAPS) (4,47–50) was assessed. Patients were considered PE+ if they had presented at least one of these experiences (N=39, 60% of tested patients; Table S1) during the psychotic episodes. Twenty-six patients (40% of tested patients) did never show these symptoms and were thus included in the PE- group. The patient groups did not differ significantly on any demographic trait (see Table 1 for the details).

Characteristic/test	PE-	PE+	p(t /χ^2)
Group size	26	39	
Gender, M/F	20/6	23/16	0.1 (2.2)
Handedness, R/L	23/3	34/3	0.4 (1.5)
Age, y	29.9 ± 10	30.5 ± 9.7	0.9 (-0.08)
Education, y	12.9 ± 2.5	12.3 ± 3.5	0.6 (0.55)
Illness duration, y	6.2 ± 7.7	5.2 ± 5.1	0.6 (0.6)
Chlorpromazine, mg/day	275 ± 247	365 ± 262	0.2 (-1.4)
PANSS total	65.5 ± 17.3	59.8 ± 16	0.2 (1.3)
PANSS positive	14 ± 4.9	13.5 ± 4.3	0.6 (0.4)
PANSS negative	17.5 ± 6	14.6 ± 5.8	*0.06 (1.9)*
Time difference between fMRI acquisition and symptom assessment, y	2.6 ± 2.1	2.7 ± 2.3	0.8 (-0.26)

Table 1. Demographic and clinical data of the patients.

Data are presented in mean ± standard deviation. 2-tailed t-tests and χ2 tests performed when appropriate. Abbreviations: M – male; F – female; R – right handed; L – left handed; y – years; PANSS – positive and negative symptom scale; PE – passivity experiences;

MR image acquisition

MRI data were acquired using a 3 Tesla scanner (Magnetom TrioTim, Siemens Medical Solutions), equipped with a 32-channel head coil. Each MRI session included a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence and a 9-minute gradient echo-planar imaging (EPI) sequence sensitive to BOLD (blood-oxygen-level-dependent) contrast. The MPRAGE acquisition had a 1mm in-plane resolution and 1.2mm slice thickness, covering 240×257×160voxels (TR=2.30ms, TE=2.98ms and TI=900ms). The functional MRI (EPI) acquisition had isotropic 3.3mm voxel size, with a 0.3mm inter-slice gap and covering a total of 64x58x32 voxels (TR=1920ms and TE=30ms). Resting-state fMRI (rs-fMRI) was recorded;

patients were lying in the scanner with eyes open, resting but awake and cognitively alert. The acquisition process resulted in a sequence of 280 BOLD images for each subject.

Image preprocessing

Standard pre-processing and data analyses were performed using SPM12 (fil.ion.ucl.ac.uk/spm/) and the functional connectivity toolbox CONN (conn-toolbox.org/) for MATLAB (mathworks.com). Functional images were corrected for slice time and motion, co-registered with a high-resolution anatomical scan, normalized into MNI space, resampled to 1.5x1.5x1.5mm3 and smoothed with a 6mm3 full-width at half maximum (FWHM) Gaussian kernel for each subject. To estimate the excessive movement, mean frame-wise displacement (FD) (51) during the scanning was estimated with the exclusion threshold of 0.5mm. The groups did not differ in terms of the movements over the scanning period (t=-0.35, p=0.7 with the mean FD of 0.18±0.09mm and 0.19±0.1 mm for PE- and PE+ groups respectively). Following the standard pipeline for confound removal of the CONN toolbox, the individual time courses of the segmented white matter and cerebrospinal fluid, the six motion parameters with rigid body transformations and their first-order derivatives, and global signal time courses were extracted and regressed out of the data. Regressions were performed for the entire time-series. The BOLD signal data were passed through a band filter (0.009-0.08 Hz). A whole-brain mask in MNI space was used to restrict number of voxels tested during data analysis.

Networks

Presence hallucination network. Presence hallucination network (PH-network; Figure 1) was defined as an overlap of the brain regions associated with the robot-induced PH with the symptomatic PH-network derived from neurological patients experiencing PH (for more details, see Bernasconi, Blondiaux et al., 2020 (25)). The overlapping areas of these two experiments are the right posterior middle temporal gyrus (pMTG right; x=54, y=-54, z=0), the right inferior frontal gyrus (IFG right; x=51, y=18, z=29) and left ventral premotor cortex (vPMC left; x=-26, y=-18, z=57). Those areas were transposed bilaterally.

Control networks. Control regions were derived by shifting each region of the PH-network but keeping the same shape and the same number of voxels as the original network (25) (Figure S1A). The areas were shifted to fit in the brain mask and do not comprise of white matter. The

areas were shifted by the following coordinates: IFG x±20 y+30 z-15; vPMC x±10 y+30 z-15; pMTG x y+30 z-15. A visual network from rs-fMRI network atlas (52) (Figure S1B) was analyzed as an additional control network. It was comprised of four regions of interest (ROIs): calcarine sulcus, left thalamus, left and right middle/ superior occipital gyri.

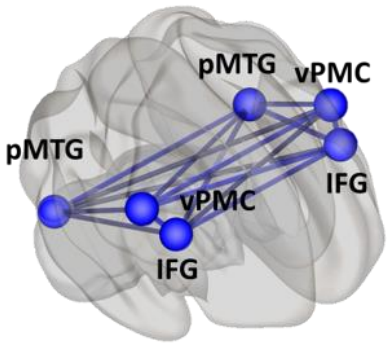

Figure 1. PH-network. Projection on the brain surface of 6 regions forming PH-network: bilaterally inferior frontal gyrus (IFG), posterior middle temporal gyrus (pMTG), ventral premotor cortex (vPMC). The network forms 15 connections (lines). Based on Bernasconi, Blondiaux et al., 2020.

Statistical analyses

Demographic and clinical variables. Possible differences in demographic and clinical variables data between the two groups of patients were assessed by unpaired t-tests and Pearson's $\chi 2$ tests, when applicable.

fMRI. Functional connectivity ROI-to-ROI analyses were conducted by extracting bivariate correlation values (z-transformed) for all possible connections within PH-network for each subject. Statistical analyses were performed in R (R-project.org/), v3.6. To investigate possible alteration in functional connectivity between groups of patients, we used linear mixed-effects models with Group (PE+, PE-) and Connection (15 connections) as fixed effects and Patients as a random effect. Post-hoc analyses for the between-group differences were performed with FDR (p=0.05) correction for multiple comparisons. Data outliers (6% of all data points) were removed based on 1.5IQR from the functional connectivity mean value for each connection. Patient's age and dose of medication were included in the analysis as the covariates of no interest due to considerable variance between the patients, which can influence functional coupling (53,54). In addition, the time difference between fMRI image acquisition and symptom evaluation was included in the model as a covariate of no interest.

To further study functional connectivity associated with PH-network, we performed seed-to-whole-brain analysis. The ROIs from the PH-network, which connections showed significant functional connectivity differences between groups, were used as seeds. Individual correlation maps were created by extracting the mean resting state BOLD time course from the seed region and correlating it with the time course of each voxel in the whole brain. Subsequently, correlation coefficients were normalized using Fisher-z-transformation to create individual single-subject maps of voxel-wise functional connectivity. The resulting maps were then entered in a second-level analysis. T-contrasts for group comparisons with $p<0.001$ peak voxel-level uncorrected and cluster level FDR $p<0.05$ corrected thresholds were analyzed. Age and medication dose of the patients were included as the covariates of no interest to control for possible confounds in functional brain coupling.

2.1.4 Results

Functional disconnection within the PH-network

We observed a significant interaction between patient group and connection (F(14,786)=3.4, p<0.0001), suggesting that individual PH-network connectivity is associated with PE. Yet, there was no significant main effect of patient group, meaning that there was no global difference of PH-network functional connectivity between groups (PE+ patients rPH_total=0.21±0.26, CI(95%)=[0.19, 0.23], PE- patients rPH_total=0.24±0.28, CI(95%) =[0.22, 0.27], F(1,56)=2.4, p=0.12). Post-hoc analysis showed that fronto-temporal connections, between the right pMTG and the right IFG (rPE+=0.235±0.172, CI(95%)=[0.17, 0.29]; rPE-=0.481±0.165, CI(95%)=[0.40, 0.56]; t=-4.1, p=0.0007) and between the right pMTG and the left IFG (rPE+=-0.029±0.223, CI(95%)=[-0.10, 0.04]; rPE-=0.152±0.206, CI(95%)=[0.07, 0.24]; t =-3.49, p=0.004) (Figure 2B) were reduced in PE+ compared to PE- patients. None of the other connections differed between groups. There also was an expected significant main effect of connection (F(14,786)=52.4, p<0.0001), meaning that the strength of functional connectivity varied between the different connections of the PH-network independent of group (55). The covariates of no interest (age, medication dose and time difference between scan acquisition and symptom evaluation) did not show significant effects (all p>0.25, see SI for the details). The same analyses in control regions (main effect of group F(1,59)=0.03, p=0.85; group by connection interaction F(14,794)=1.4 p=0.14; Figure S3) and in a visual control network (main effect of group F(1,54)=0.57, p=0.45; group by connection interaction F(5,276)=0.53, p=0.75; Figure S4) revealed no significant differences between the two groups.

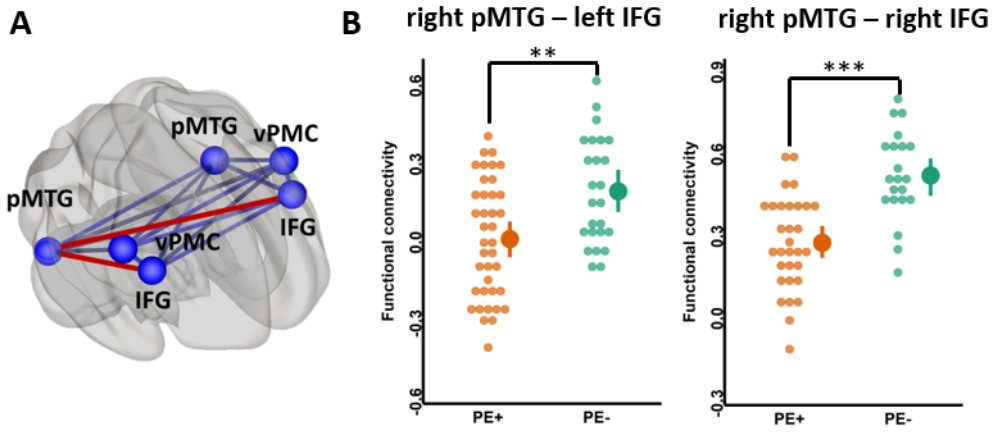

Figure 2. Functional disconnectivity within the PH- network comparing patients with (PE +) and without (PE -) passivity experiences. A. Abnormal fronto-temporal connections are marked in red and were

decreased in PE+ patients versus PE- patients. **B.** Functional connectivity between the right posterior middle temporal gyrus (pMTG) and the left inferior frontal gyrus (IFG; left plot), and the pMTG and the right IFG (right plot). Post-hoc FDR corrected at the threshold of p=0.05. **p<0.01, ***p<0.001. Dots represent the individual connectivity values of each patient.

Extended PH-network functional connectivity changes

To investigate whether there are any global changes in connectivity associated with the PH-network that differed between groups, we conducted seed-based analyses from the three nodes forming the two altered connections in the PH-network indicated by the previous connectivity analysis. These three regions used as seeds were right pMTG, left IFG, and right IFG. With the right pMTG as seed, we observed a statistically significant decrease in functional connectivity between the right middle frontal gyrus and the left inferior frontal gyrus in the PE+ group compared to the PE- group. Both areas partly overlapped with the ROIs of the PH-network (108 voxels with the left IFG, two voxels with the right IFG; Figure 3A). Using the right IFG as a seed, we observed a statistically significant decrease in functional coupling with the right medial superior frontal gyrus and the left Heschl's gyrus (superior temporal gyrus) in the PE+ group versus PE- group (Figure 3B). Seeding from left IFG revealed a statistically significant increase in functional coupling with the left putamen and decrease in functional coupling with the left lateral occipital cortex (inferior occipital gyrus), and the right middle temporal gyrus in the PE+ versus PE- group (Figure 3C). We note that the cluster in the right middle temporal gyrus was part of the PH-network area (59 voxels overlap with the right pMTG; Figure 3A). The details of all clusters are described in Table 2.

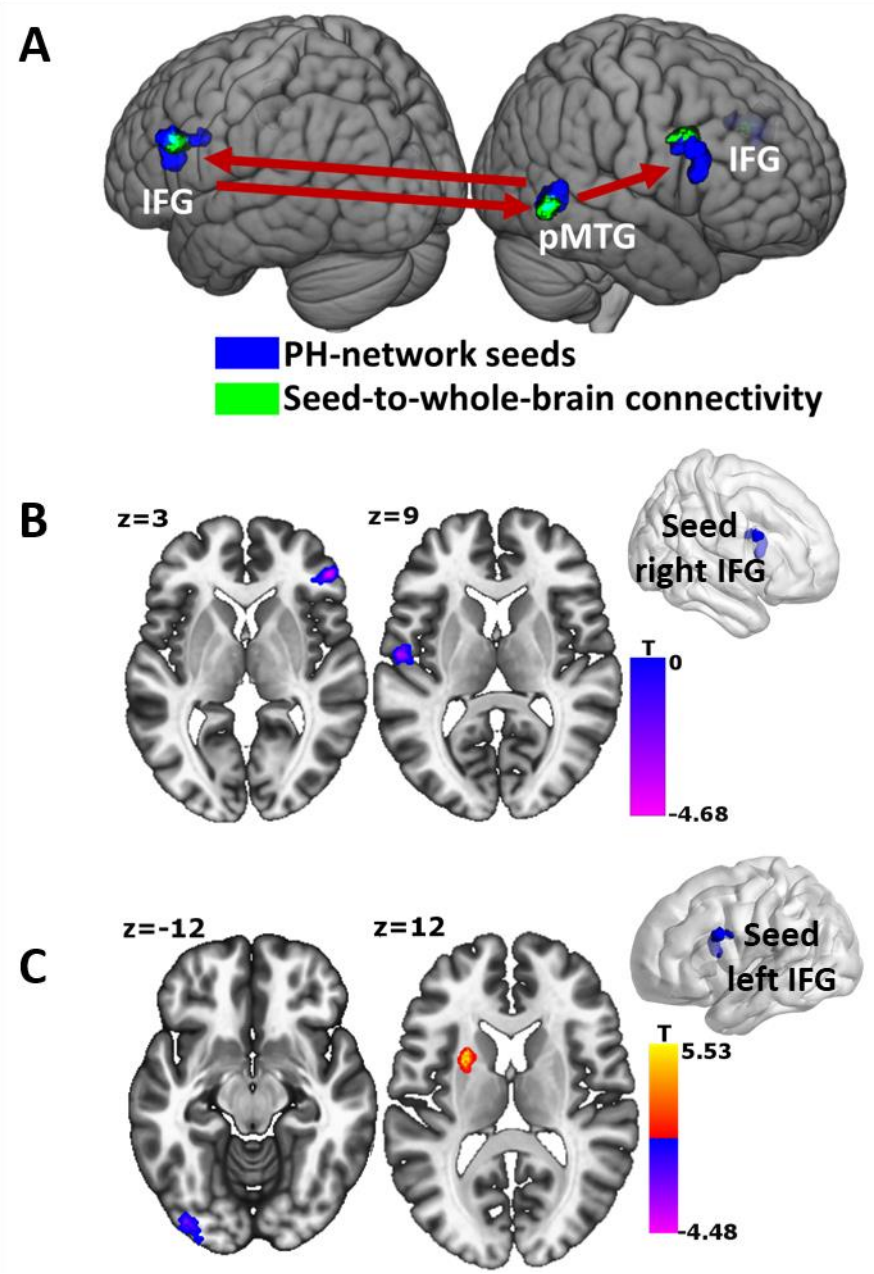

Figure 3. Functional connectivity changes in PE+ versus PE- patients seeding from the PH-network areas to the whole brain. A. PH-network seeds (in blue) were traced back during whole-brain functional connectivity analysis (areas in green). The red arrows represent from which seed (blue) the decreased functional connectivity in PE+ patients were observed **B.** Decreased functional connectivity in PE+ patients seeding from the right IFG with the right medial superior frontal gyrus and the left Heschl's gyrus **C.** Decreased functional connectivity in PE+ patients seeding from the left IFG with the left inferior occipital gyrus and increased functional connectivity with the left putamen. Voxel level $p<0.001$ uncorrected, cluster threshold at $p<0.05$ FDR corrected.

Seed-to-whole-brain PE+ vs. PE-				MNI coordinates				
BA	Anatomic Label		k (vox)	x	y	z	β	T
	right pMTG							
9	Middle frontal gyrus	R	189	35	06	32	-0.22	-4.58
9	Inferior frontal gyrus	L	161	-53	17	27	-0.22	-4.47
	right IFG							
8	Medial superior frontal gyrus (frontal pole)	R	137	48	39	03	-0.22	-4.64
43, 22	Heschl's gyrus (part of superior temporal gyrus)	L	149	-57	-11	09	-0.17	-4.06
	left IFG							
	Putamen	L	178	-24	08	14	0.14	5.34
18	Lateral occipital cortex, inferior division (inferior occipital gyrus)	L	211	-39	-87	-12	-0.16	-4.18
21, 37	Middle temporal gyrus, temporooccipital part	R	147	63	-53	-03	-0.19	-4.13

Table 2. Details of the clusters from seed-to-whole-brain functional connectivity analysis.

BA– Broadman area, k– cluster size in voxels, PE– passivity experiences. Voxel level p<0.001 uncorrected, cluster threshold at p<0.05 FDR-corrected

2.1.5 Discussion

Investigating functional connectivity changes within the PH-network in psychotic patients with and without PE, we observed an alteration of fronto-temporal functional connectivity within the PH-network that was characterized by decreased connectivity in PE+ compared to PE- patients. Additional results showed that this connectivity pattern is region-specific and limited to the PH-network as analysis of two control networks did not reveal any significant group differences. These data were corroborated and extended by seed-to-the-whole-brain connectivity, allowing us to trace back the fronto-temporal connectivity decreases in the PH-network without any a priori regional restriction of the connections.

Altered resting-state functional connectivity in psychotic patients has been observed in numerous studies (for review see (40,56–58)) and it has been proposed that psychotic symptoms are related to decreases in functional connectivity formulated, for example, in the disconnection hypothesis (39,40,59,60). Our findings are compatible with and extend this proposal, as we observed reduced connectivity in PE+ patients that was restricted to the PH-network and concerned fronto-temporal connectivity within this network. Interestingly, fronto-temporal disconnectivity has previously been associated with impaired sensorimotor integration in patients with schizophrenia (41–43). As PE (4–6) and PH (4,24) have also been associated with sensorimotor and prediction mechanisms, our finding of fronto-temporal disconnectivity in the PH-network in PE patients associates the brain mechanism of PH with those of PE and psychosis. Fronto-temporal disconnection of the PH-network in psychotic patients extends recent work investigating symptomatic PH in other patient populations, such as those suffering from Parkinson's disease (25) and dementia with Lewy bodies (31), two neurological neurodegenerative diseases that are frequently associated with hallucinations and psychosis. Thus, Parkinson's disease patients with symptomatic PH had decreased functional fronto-temporal connectivity (between the left pMTG and left IFG) (25) compared to Parkinson's disease patients without PH. Moreover, PH-network functional connectivity could be used to predict the occurrence of PH as a symptom during daily life and these patients were found to have abnormal elevated sensitivity to sensorimotor stimulation (25). A PET study in dementia with Lewy bodies patients (31) (who frequently experience PH) reported reduced glucose metabolism in fronto-temporal cortical areas (in patients with versus without PH), partly overlapping with the altered fronto-temporal connections in the

present study. Taken together, the present findings suggest that fronto-temporal connectivity changes are not only of relevance to study PH, their neural mechanisms and disruption in neuropsychiatric diseases, but are also disrupted in psychiatric patients with psychosis suffering from a larger range of PE, extending the disconnection hypothesis to PH (41–43,61).

One of the most frequent PE in psychosis is AVH (27), often in the form of voices arguing and commenting about the patient. Among the many accounts for AVHs (62,63), a prominent one, that is of relevance for the present work on psychosis and PH, has argued that AVH are caused by altered self-monitoring associating loss of self-attribution (inner speech is not perceived as self-generated; negative aspect) with misattribution to an external agent (inner speech perceived as that of another person; positive aspect) (64,65). How are AVH related to PH and to the neural mechanisms of PH? Recent studies were able to link PH and mild psychotic states to altered sensorimotor processing and changes in voice perception. This was found in first-episode psychosis patients (4) as well as healthy subjects (26). Thus, when exposed to specific sensorimotor conflicts giving rise to PH, first-episode psychosis patients (with PE) misattributed their voice to an external agent. These misattribution errors were absent in patients without PE, showing that sensorimotor stimulations leading to a mental state mimicking PH is associated with alterations in auditory-verbal self-monitoring (4) and, potentially, with the PH network.

Our findings, applying seed-to-whole-brain analysis, provide further evidence for the proposal that the PH, related sensorimotor mechanisms, and the PH-network are of importance in AVH. When the affected PH-network areas were used as seeds to the whole-brain, we observed altered functional connectivity in key auditory regions. More specifically, we link the PH to auditory processing in psychosis patients by revealing altered functional connectivity between the PH-network and Heschl's gyrus. We found decreased functional connectivity (PE+ versus PE- group) between the right IFG and left Heschl's gyrus that is part of the primary auditory cortex and has frequently been reported to have altered functional connectivity in psychotic patients with AVH (60,66,67). Moreover, we observed increased functional connectivity between the left IFG and the left putamen in PE+ patients, a subcortical structure that has also been linked to AVH (68–70). AVH is one of the most occurring symptoms in psychotic patients (27) and indeed, in this study, one of the inclusion criteria for the PE+ group was the presence of AVH, where 56% of the patients reported to suffer from this symptom (see Table

S1). These findings therefore associate the PH-network with AVH and extend proposals that the PH and related network is important for the positive aspect of AVH and PE (4,24,26). The seed-to-whole-brain data also corroborate behavioral evidence from specific sensorimotor stimulations that have been shown to not only induce experimentally-controlled PH, but also changes in auditory perception (4,26).

The current study had several limitations, which may restrict the interpretation of the results. First, the evaluation of the symptoms was considered as a lifetime occurrence. Although detailed interviews were carried out about all PE symptoms, we only had access to MRI data ranging over a large period of time. Future work should perform the clinical interview and scanning with a shorter and fixed delay. Second, future studies should directly evaluate the occurrence of PH among the tested patients.

Conclusions

To summarize, we show that the brain regions and functional connectivity within the PH-network that was determined independently from the present study (experimentally-induced PHs in healthy participants and symptomatic PHs in neurological patients) (24,25) are of relevance in psychiatric patients suffering from psychosis characterized by PE. We found evidence for a specific decrease in fronto-temporal functional connectivity in psychotic patients with PE and that this decrease was driven by decreased connectivity between the right pMTG and bilateral IFG. Besides, we show that the PH-network's altered connectivity is associated with changes in connectivity with Heschl's gyrus and putamen, two areas previously associated with AVH and altered auditory-verbal processing, further supporting the importance of the neural mechanisms of PH and PH-network in psychosis and PE. Based on the present data, future neuroimaging studies evaluating the sensitivity of psychotic patients to robot-induced PH (24,25) and how this affects auditory-verbal processing (4,26) will be necessary. This may allow for more detailed behavioral evaluations based on robot-induced mental states and their respective brain networks, providing improved biomarkers for diagnosis and therapy.

2.1.6 References

1. Lysaker PH, Lysaker JT. Narrative Structure in Psychosis. Theory Psychol. 2002 Apr 17;12(2):207–20.
2. Schneider K. [Primary & secondary symptoms in schizophrenia]. Fortschr Neurol Psychiatr Grenzgeb. 1957 Sep;25(9):487–90.
3. Kendler KS, Mishara A. The Prehistory of Schneider's First-Rank Symptoms: Texts from 1810 to 1932. Schizophr Bull. 2019;45(5):971–90.
4. Salomon R, Progin P, Griffa A, Rognini G, Do KQ, Conus P, et al. Sensorimotor Induction of Auditory Misattribution in Early Psychosis. Schizophr Bull. 2020 Feb 11;1–8. article/doi/10.1093/schbul/sbz136/5733158
5. Graham-Schmidt KT, Martin-Iverson MT, Waters FAV. Self- and other-agency in people with passivity (first rank) symptoms in schizophrenia. Schizophr Res. 2018;192:75–81.
6. Waters FAV, Badcock JC, Dragović M, Jablensky A. Neuropsychological functioning in schizophrenia patients with first-rank (passivity) symptoms. Psychopathology. 2009;42(1):47–58.
7. Blakemore SJ, Smith J, Steel R, Johnstone CE, Frith CD. The perception of self-produced sensory stimuli in patients with auditory hallucinations and passivity experiences: evidence for a breakdown in self-monitoring. Psychol Med. 2000;30(5):1131–9.
8. Ford JM, Mathalon DH. Efference Copy, Corollary Discharge, Predictive Coding, and Psychosis. Biol Psychiatry Cogn Neurosci Neuroimaging. 2019;4(9):764–7.
9. Blakemore SJ, Goodbody SJ, Wolpert DM. Predicting the Consequences of Our Own Actions: The Role of Sensorimotor Context Estimation. J Neurosci. 1998;18(18):7511–8.
10. Ford JM, Palzes VA, Roach BJ, Mathalon DH. Did I Do That? Abnormal Predictive Processes in Schizophrenia When Button Pressing to Deliver a Tone. Schizophr Bull. 2014 Jul;40(4):804–12.
11. Frith CD. Can a Problem With Corollary Discharge Explain the Symptoms of Schizophrenia? Biol Psychiatry Cogn Neurosci Neuroimaging. 2019;4(9):768–9.
12. Sousa P, Swiney L. Thought insertion: Abnormal sense of thought agency or thought endorsement? Phenomenol Cogn Sci. 2013;12(4):637–54.
13. Martin JR, Pacherie E. Out of nowhere: Thought insertion, ownership and context-integration. Conscious Cogn. 2013;22(1):111–22.
14. Taylor MA. Schneiderian First-Rank Symptoms and Clinical Prognostic Features in Schizophrenia. Arch Gen Psychiatry. 1972;26(1):64–7.
15. Koehler K. First rank symptoms of schizophrenia: Questions concerning clinical boundaries. Br J Psychiatry. 1979;134(3):236–48.
16. Schneider K. Clinical psychopathology. Grune & Stratton; 1959.
17. Mullins S, Spence S a. Re-examining thought insertion: Semi-structured literature review and conceptual analysis. Br J Psychiatry. 2014;182:293–8.
18. Gallagher S. Neurocognitive models of schizophrenia: A neurophenomenological critique. Psychopathology. 2004;37(1):8–19.
19. Fletcher PC, Frith CD. Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. Nat Rev Neurosci. 2009;10(1):48–58.
20. Frith C. The Self in Action: Lessons From Delusions of Control. Conscious Cogn. 2005;14(4):752–770.

21. Frith CD, Done DJ. Experiences of alien control in schizophrenia reflect a disorder in the central monitoring of action. Psychol Med. 1989 May 9;19(2):359–63.
22. Bansal S, Ford JM, Spering M. The function and failure of sensory predictions. Ann N Y Acad Sci. 2018;1426(1):199–220.
23. Sommer IE, Selten JP, Diederen KM, Blom JD. Dissecting auditory verbal hallucinations into two components: Audibility (Gedankenlautwerden) and alienation (thought insertion). Psychopathology. 2010;43(2):137–40.
24. Blanke O, Pozeg P, Hara M, Heydrich L, Serino A, Yamamoto A, et al. Neurological and robot-controlled induction of an apparition. Curr Biol. 2014;24(22):2681–6.
25. Bernasconi F, Blondiaux E, Potheegadoo J, Stripeikyte G, Pagonabarraga J, Bejr-Kasem H, et al. Sensorimotor hallucinations in Parkinson' s disease. bioRxiv. 2020;
26. Orepic P, Rognini G, Kannape OA, Faivre N. Sensorimotor conflicts induce somatic passivity and louden quiet voices in healthy listeners Running title : Sensorimotor basis of voice perception. 2020;41(0):1–32.
27. Llorca PM, Pereira B, Jardri R, Chereau-Boudet I, Brousse G, Misdrahi D, et al. Hallucinations in schizophrenia and Parkinson's disease: an analysis of sensory modalities involved and the repercussion on patients. Sci Rep. 2016;6(1):38152.
28. Blanke O. Multisensory brain mechanisms of bodily self-consciousness. Nat Rev Neurosci. 2012;13(August):556–71. Available from: http://www.nature.com/doifinder/10.1038/nrn3292
29. Blanke O, Slater M, Serino A. Behavioral, Neural, and Computational Principles of Bodily Self-Consciousness. Neuron. 2015;88(1):145–66.
30. Fénelon G, Soulas T, De Langavant LC, Trinkler I, Bachoud-Lévi A-C. Feeling of presence in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2011 Nov;82(11):1219–24.
31. Nicastro N, Eger AF, Assal F, Garibotto V. Feeling of presence in dementia with Lewy bodies is related to reduced left frontoparietal metabolism. Brain Imaging Behav. 2018.
32. Nagahama Y, Okina T, Suzuki N, Matsuda M. Neural correlates of psychotic symptoms in dementia with Lewy bodies. Brain. 2010;133(2):557–67.
33. Arzy S, Seeck M, Ortigue S, Spinelli L, Blanke O. Induction of an illusory shadow person. Nature. 2006;443(7109):287.
34. Reckner E, Cipolotti L, Foley JA. Presence Phenomena in Parkinsonian Disorders: Phenomenology and Neuropsychological Correlates. Int J Geriatr Psychiatry. 2020.
35. Boes AD, Prasad S, Liu H, Liu Q, Pascual-Leone A, Caviness VS, et al. Network localization of neurological symptoms from focal brain lesions. Brain. 2015;138(10):3061–75.
36. Hara M, Salomon R, van der Zwaag W, Kober T, Rognini G, Nabae H, et al. A novel manipulation method of human body ownership using an fMRI-compatible master-slave system. J Neurosci Methods. 2014;235:25–34.
37. Friston KJ. The disconnection hypothesis. Schizophr Res. 1998;30(2):115–25.
38. Hahamy A, Calhoun V, Pearlson G, Harel M, Stern N, Attar F, et al. Save the Global: Global Signal Connectivity as a Tool for Studying Clinical Populations with Functional Magnetic Resonance Imaging. Brain Connect. 2014 Aug;4(6):395–403.
39. Skudlarski P, Jagannathan K, Anderson K, Stevens MC, Calhoun VD, Skudlarska BA, et al. Brain Connectivity Is Not Only Lower but Different in Schizophrenia: A Combined Anatomical and Functional Approach. Biol Psychiatry. 2010;68(1):61–9.

40. Karbasforoushan H, Woodward ND. Resting-State Networks in Schizophrenia. Curr Top Med Chem. 2013;12(21):2404–14.
41. Lawrie SM, Buechel C, Whalley HC, Frith CD, Friston KJ, Johnstone EC. Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations. Biol Psychiatry. 2002;51(12):1008–11.
42. Friston K, Brown HR, Siemerkus J, Stephan KE. The dysconnection hypothesis (2016). Schizophr Res. 2016;176(2–3):83–94.
43. Frith CD, Blakemore SJ, Wolpert DM. Explaining the symptoms of schizophrenia: Abnormalities in the awareness of action. Brain Res Rev. 2000;31(2–3):357–63.
44. American Psychiatric Association. DSM-IV. Diagnostic and Statistical Manual of Mental Disorders 4th edition TR. 2000.
45. Baumann PS, Crespi S, Marion-Veyron R, Solida A, Thonney J, Favrod J, et al. Treatment and early intervention in psychosis program (TIPP-Lausanne): Implementation of an early intervention programme for psychosis in Switzerland. Early Interv Psychiatry. 2013;7(3):322–8.
46. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261–76.
47. Schnell K, Heekeren K, Daumann J, Schnell T, Schnitker R, Möller-Hartmann W, et al. Correlation of passivity symptoms and dysfunctional visuomotor action monitoring in psychosis. Brain. 2008;131(10):2783–97.
48. Franck N, O'Leary DS, Flaum M, Hichwa RD, Andreasen NC. Cerebral Blood Flow Changes Associated With Schneiderian First-Rank Symptoms in Schizophrenia. J Neuropsychiatry Clin Neurosci. 2002 Aug;14(3):277–82.
49. Farrer C, Franck N, Frith CD, Decety J, Georgieff N, D'Amato T, et al. Neural correlates of action attribution in schizophrenia. Psychiatry Res Neuroimaging. 2004 May;131(1):31–44.
50. Andreasen NC. Scale for the Assessment of Positive Symptoms (SAPS). Br J Psychiatry Suppl. 1984;(7):49–58.
51. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage. 2012;59(3):2142–54.
52. Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD. Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cereb Cortex. 2012;22(1):158–65.
53. Ferreira LK, Regina ACB, Kovacevic N, Martin MDGM, Santos PP, Carneiro CDG, et al. Aging effects on whole-brain functional connectivity in adults free of cognitive and psychiatric disorders. Cereb Cortex. 2016;26(9):3851–65.
54. H. Roder C, Marie Hoogendam J, M. van der Veen F. FMRI, Antipsychotics and Schizophrenia. Influence of Different Antipsychotics on BOLD-Signal. Curr Pharm Des. 2010;16(18):2012–25.
55. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007;8(9):700–11.
56. González-Vivas C, Soldevila-Matías P, Sparano O, García-Martí G, Martí-Bonmatí L, Crespo-Facorro B, et al. Longitudinal studies of functional magnetic resonance imaging in first-episode psychosis: A systematic review. Eur Psychiatry. 2019;59:60–9.

57. Satterthwaite TD, Baker JT. How can studies of resting-state functional connectivity help us understand psychosis as a disorder of brain development? Curr Opin Neurobiol. 2015;30(October 2014):85–91.
58. Mwansisya TE, Hu A, Li Y, Chen X, Wu G, Huang X, et al. Task and resting-state fMRI studies in first-episode schizophrenia: A systematic review. Schizophr Res. 2017;189:9–18.
59. Crossley N a., Mechelli A, Fusar-Poli P, Broome MR, Matthiasson P, Johns LC, et al. Superior temporal lobe dysfunction and frontotemporal dysconnectivity in subjects at risk of psychosis and in first-episode psychosis. Hum Brain Mapp. 2009;30(12):4129–37.
60. Oertel-Knöchel V, Knöchel C, Matura S, Stäblein M, Prvulovic D, Maurer K, et al. Association between symptoms of psychosis and reduced functional connectivity of auditory cortex. Schizophr Res. 2014;160(1–3):35–42.
61. Frith C. The neural basis of hallucinations and delusions. Comptes Rendus - Biol. 2005;328(2):169–75.
62. Humpston CS, Adams RA, Benrimoh D, Broome MR, Corlett PR, Gerrans P, et al. From Computation to the First-Person: Auditory-Verbal Hallucinations and Delusions of Thought Interference in Schizophrenia-Spectrum Psychoses. Schizophr Bull. 2019;45(1):S56–66.
63. Cho R, Wu W. Mechanisms of auditory verbal hallucination in schizophrenia. Front Psychiatry. 2013;4(NOV):1–8.
64. Jones SR, Fernyhough C. Neural correlates of inner speech and auditory verbal hallucinations: A critical review and theoretical integration. Clin Psychol Rev. 2007;27(2):140–54.
65. Tracy DK, Shergill SS. Mechanisms Underlying Auditory Hallucinations-Understanding Perception without Stimulus. Brain Sci. 2013;3(2):642–69.
66. Shinn AK, Baker JT, Cohen BM, Öngür D. Functional connectivity of left Heschl's gyrus in vulnerability to auditory hallucinations in schizophrenia. Schizophr Res. 2013;143(2–3):260–8.
67. Dierks T, J Linden DE, Jandl M, Formisano E, Goebel R. Activation of Heschl's Gyrus during Auditory Hallucinations of these studies could directly differentiate between the hallucinatory and nonhallucinatory states within one scanning session. Because of this restriction, they did. Neuron. 1999;22:615–21.
68. Cui LB, Liu K, Li C, Wang LX, Guo F, Tian P, et al. Putamen-related regional and network functional deficits in first-episode schizophrenia with auditory verbal hallucinations. Schizophr Res. 2016;173(1–2):13–22.
69. Hoffman RE, Fernandez T, Pittman B, Hampson M. Elevated functional connectivity along a corticostriatal loop and the mechanism of auditory/verbal hallucinations in patients with schizophrenia. Biol Psychiatry. 2011;69(5):407–14.
70. Hoffman RE, Hampson M. Functional connectivity studies of patients with auditory verbal hallucinations. Front Hum Neurosci. 2012;6(January):1–7.

2.1.7 Supplementary Information

ROI-to-ROI analysis

PH-network. Linear mixed model analyses were performed for the PH-network investigation (all connections' functional connectivity is depicted in Figure S2). This model included covariates of no interest which did not have significant effect to the functional connectivity differences between the groups: patient's age ($F(1,56) = 0.23$, $p = 0.63$), dosage of medication ($F(1,56) = 0.04$, $p = 0.84$) and time difference between fMRI acquisition and symptom evaluation ($F(1,55) = 1.18$, $p = 0.28$).

Control networks. Control networks' functional connectivity in patients with psychosis were analyzed applying the same analysis as for the PH-network investigation (see methods section). We formed a control network where we controlled for the number of voxels and shape of the PH-network ROIs. We shifted each PH-network ROI in the coordinate system by x ± 0 to 20 voxels, y + 30 voxels, z - 15 voxels and thus formed a new network comprising of bilateral inferior middle temporal gyrus (iMTG <- pMTG), middle frontal gyrus (MFG <- vPMC) and orbital superior frontal gyrus (oSFG <- IFG) (see Figure S1 A). Statistical analysis in control regions which were derived by shifting PH-network areas showed no significant effect of group ($F(1,59) = 0.10$, $p = 0.74$; PE+ r_total = 0.09 ± 0.36, CI(95%) = [0.05, 0.12]; PE- r_total = 0.09 ± 0.35, CI(95%) = [0.06, 0.13]) nor interaction of group and connection ($F(1,14) = 1.4$ $p=0.15$). Main effect connections ($F(14,794) = 100.6$, $p<0.0001$) was significant. Covariates of no interest (patient's age ($F(1,56) = 0.06$, $p = 0.8$) and dosage of medication ($F(1,56) = 0.77$, $p = 0.15$) did not have significant effect.

Visual network from resting state fMRI network atlas (Shirer et al., 2012) was analyzed as a second control (Figure S1 B). The visual network was composed of a the calcarine sulcus, left thalamus, left and right middle / superior occipital gyri. Statistical analysis in visual network showed no significant effect of group ($F(1,54) = 0.57$, $p = 0.45$; PE+ r_total = 0.38 ± 0.42, CI(95%) = [0.32, 0.44]; PE- r_total = 0.36 ± 0.44, CI(95%) = [0.29, 0.43]) and group by connection interaction ($F(5,276) = 0.53$, $p=0.75$). Main effect connections ($F(5,276) = 278.3$, $p < 0.001$) were significant. Patients' age which was used in the model as a covariate of no interest had significant effect: $F(1,1) = 5.92$, $p = 0.02$ while dosage of medication had no significant effect ($F(1,1) = 0.60$, $p = 0.44$).

Subject	Auditory verbal hallucination	Thought insertion	Somatic passivity	Thought withdrawal	Thought broadcasting	Other passivity symptoms
1	+	+	+		+	+
2	+	+				
3	+	+				+
4	+	+	+	+	+	+
5		+				+
6			+			
7			+			
8	+	+			+	+
9	+		+			+
10						+
11		+				+
12	+		+			+
13	+	+	+	+		+
14	+		+			
15		+				
16					+	
17		+			+	
18					+	
19	+	+	+		+	+
20		+			+	+
21		+				+
22		+	+			+
23	+					+
24	+	+	+	+	+	+
25	+	+			+	+
26		+	+		+	
27		+	+			+
28	+	+		+	+	+
29	+	+	+		+	+
30	+	+				+
31	+					
32	+	+	+			+
33	+				+	+
34	+	+	+			+
35		+				+
36	+	+		+	+	
37		+				
38	+	+		+	+	+
39			+	+		+
Total	**22**	**28**	**18**	**8**	**18**	**27**

Table S1. Passivity experiences per subject in PE+ group.

Presence of the symptom is marked by '+'. Total number of patients having each symptom is depicted at the bottom of the table.

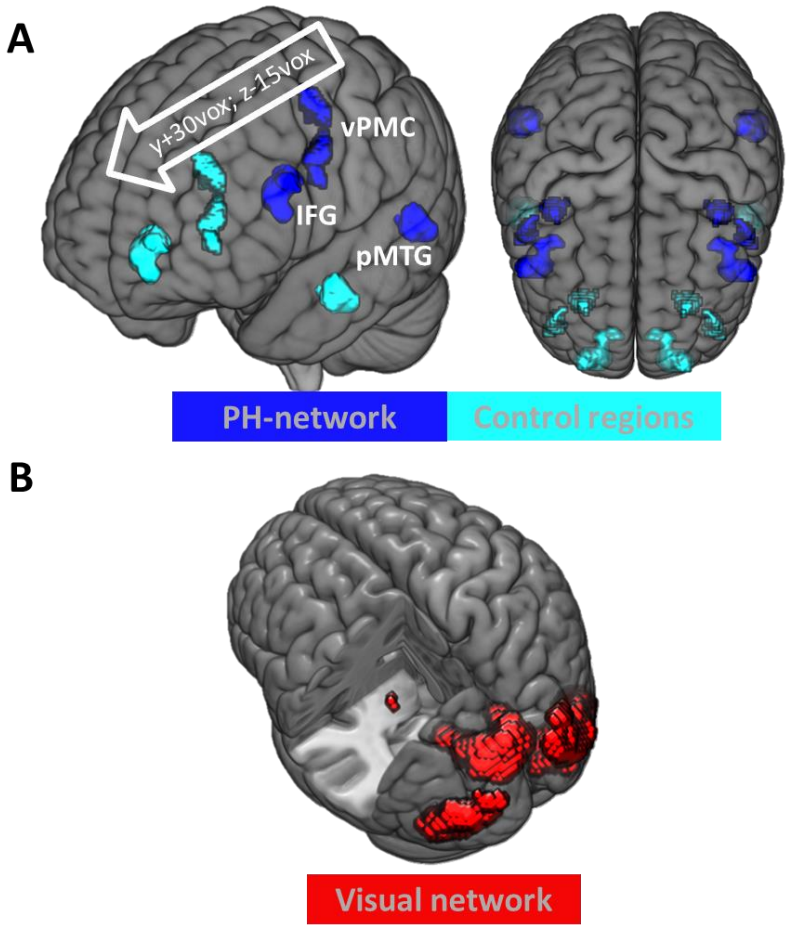

Figure S1. Control networks. A. PH-network (dark blue) and shifted regions of PH-network (light blue) projection on the brain surface left hemisphere and top brain surface view. IFG - inferior frontal gyrus, pMTG - posterior middle temporal gyrus, vPMC - ventral premotor cortex. **B.** Visual network projection on the brain surface.

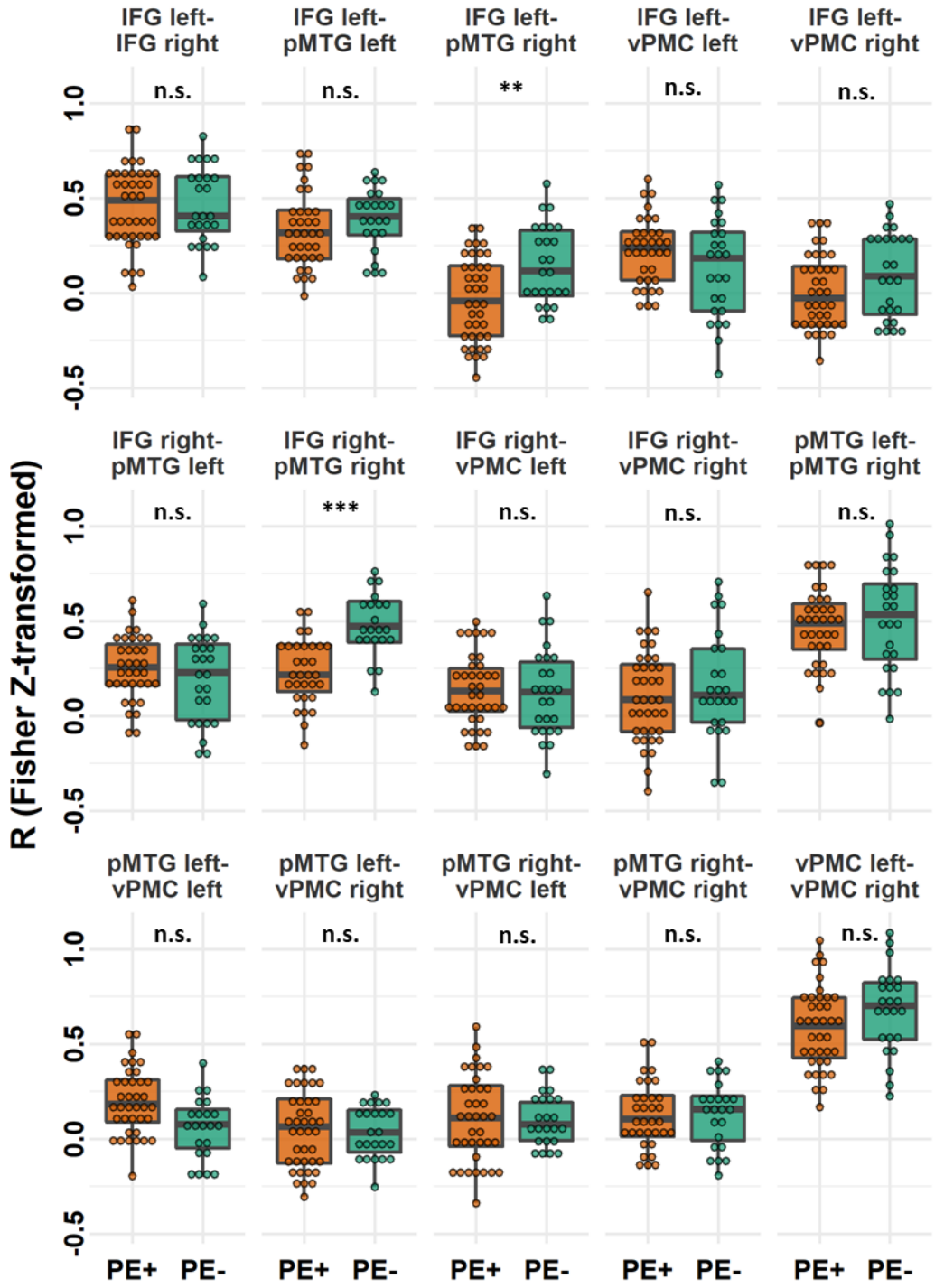

Figure S2. Functional connectivity of 15 PH-network connections. IFG - inferior frontal gyrus, pMTG - posterior middle temporal gyrus, vPMC - ventral premotor cortex. n.s – not significant; **p<0.01, ***p<0.001 FDR corrected for multiple comparisons. Dots represent individual connectivity values.

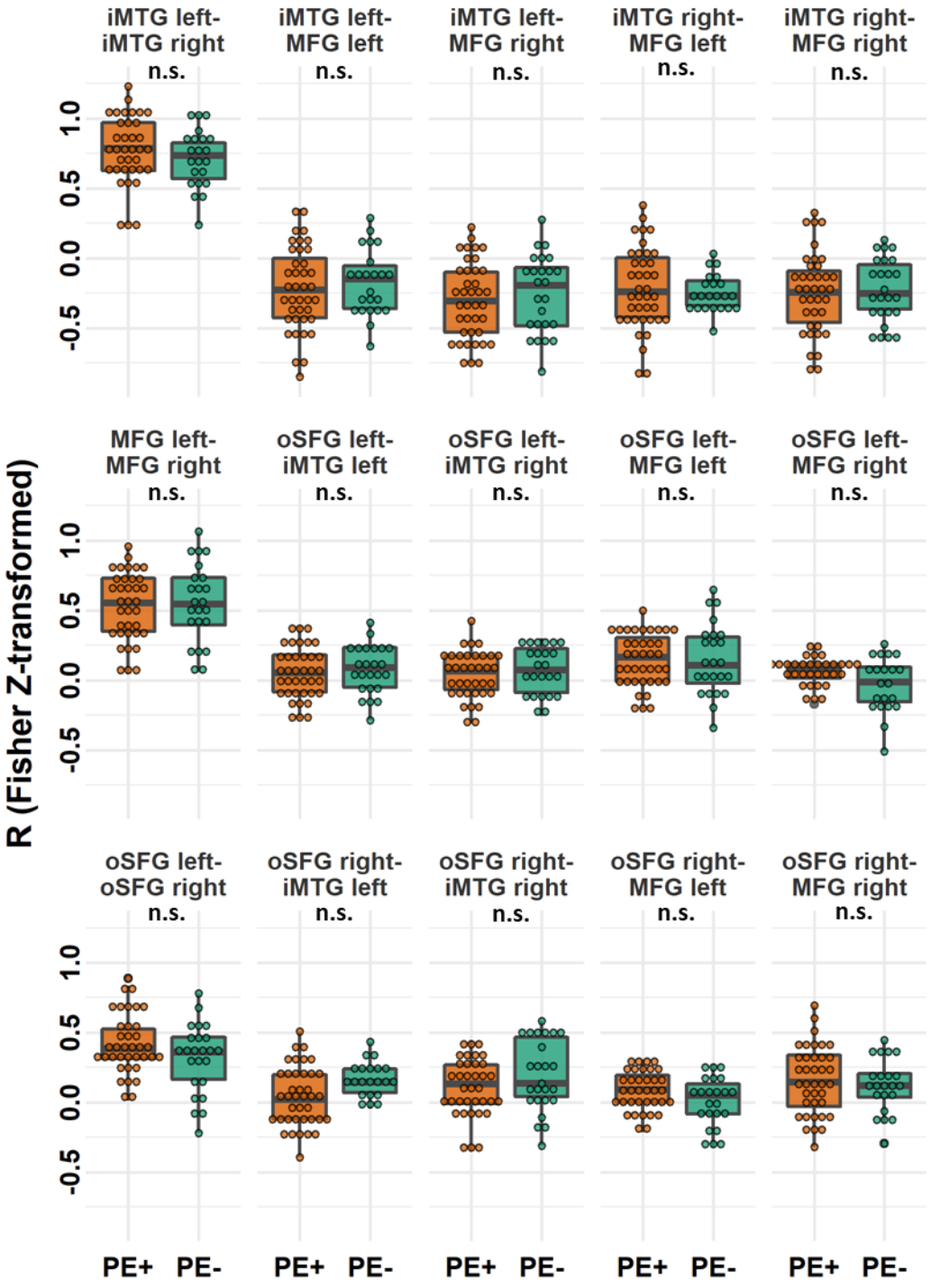

Figure S3. Functional connectivity of 15 control regions' connections. No significant differences between PE+ versus PE- groups were observed. Control regions were derived by shifting PH-network ROIs. iMTG - inferior middle temporal gyrus, MFG - middle frontal gyrus, oSFG - orbital superior frontal gyrus. n.s – not significant. Dots represent individual connectivity values.

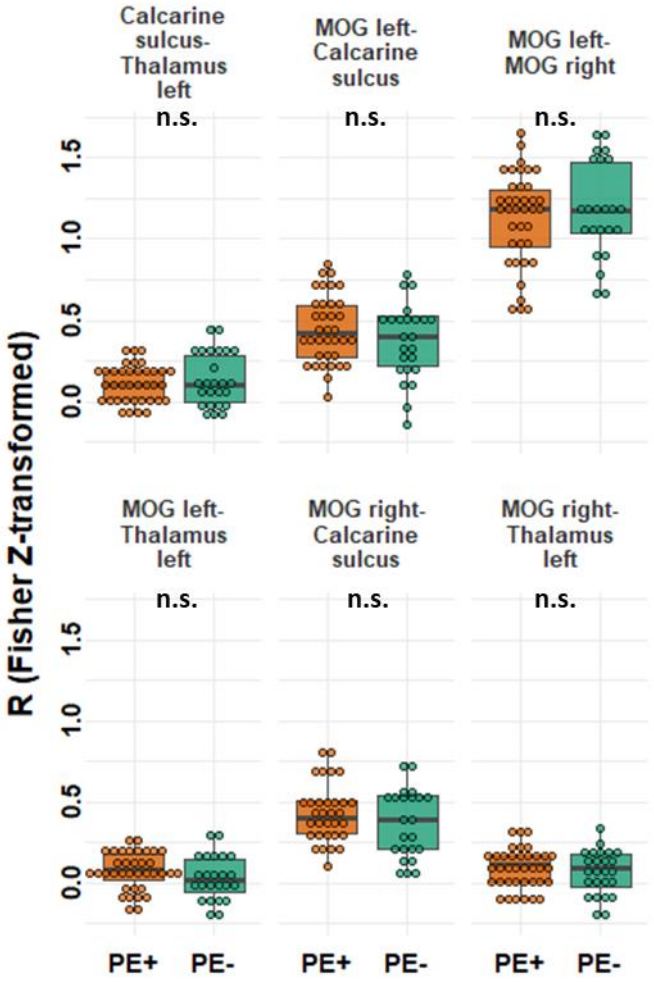

Figure S4. Functional connectivity of 6 visual control network connections. No significant differences between PE+ versus PE- groups were observed. MOG – middle occipital gyrus. n.s – not significant. Dots represent individual connectivity values.

2.2 STUDY 2: INDIVIDUALS WITH THE 22Q11.2 DELETION SYNDROME SHOW LACK OF SENSITIVITY TO SENSORIMOTOR CONFLICTS

Authors

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Disclosure statement

The authors report no conflict of interest.

2.2.1 Abstract

Objective: The 22q11.2 deletion syndrome (22q11DS) represents one of the highest risk factors for developing schizophrenia. About 30% of individuals with 22q11DS develop symptoms such as hallucinations, thought disorders and passivity experiences (PE) including loss of agency (LoA). These symptoms might arise from abnormal sensorimotor processing leading to the misattribution of self-generated actions to external sources.

Methods: We used, recently developed experimental paradigms with robotic devices generating sensorimotor conflicts to induce in a safe and controlled manner mild to moderate experiences phenomenologically similar to specific psychotic symptoms (PH, PE and LoA). We assessed the sensitivity of 22q11DS subjects to sensorimotor conflicts and their proneness in experiencing robot-induced PH and related PE as compared to age-matched controls. In addition, we evaluated the functional connectivity at rest within a network recently associated to PH (bilateral ventral premotor cortex (vPMC), inferior frontal gyrus (IFG) and posterior middle temporal gyrus (pMTG)).

Results: We showed a lack of sensitivity in sensorimotor modulation for LoA in 22q11DS subjects compared to controls. With varying degrees of sensorimotor conflicts, 22q11DS subjects again showed a lack of delay dependency in experiencing robot-induced PH and PE. The neuroimaging analysis revealed a specific disconnection between the right pMTG and right IFG, right pMTG and right vPMC and bilateral pMTG. Correlations with neuropsychological data for executive functions were also examined.

Conclusions: The present study highlights a fronto-temporal disconnection in 22q11DS subjects asymptomatic for psychosis, and a lack of sensorimotor modulation compared to controls.

Keywords: velocardiofacial syndrome; functional connectivity; presence hallucination; passivity experiences; loss of agency; executive dysfunctions.

2.2.2 Introduction

The 22q11.2 microdeletion syndrome (22q11DS or velocardiofacial syndrome) is a well-established genetic condition that gives rise to very heterogeneous clinical manifestations. Important developmental delays, cognitive deficits and neuropsychiatric disorders evince structural and functional brain abnormalities in individuals with 22q11DS (1,2). Importantly, the 22q11DS represents one of the highest genetic risk factors for developing schizophrenia (3–5). Up to 60% of the individuals with 22q11DS have subthreshold psychotic symptoms as from late children or early adolescence, and 25% to 30% of the individuals develop definite symptoms such as hallucinations, delusions or passivity symptoms (thought disorders, loss of agency (LoA) or somatic passivity) (6–8).

One possible explanation for the occurrence of hallucinations and passivity symptoms in schizophrenia resides in the fronto-temporal disconnection hypothesis supported by the forward model (9–11). This model posits that deficits in self-monitoring are linked to abnormal sensorimotor integration and predictions in schizophrenia resulting in the misattribution of one's own actions to an external sources, thus leading to abnormal perceptions such as hallucinations and passivity experiences (e.g., LoA, delusion of control, feeling of an alien presence) (10,12–14).

In 22q11DS, deficits in sensorimotor processing have been studied in the visual and auditory domain, and mainly linked with deficits in executive functions (working memory, visual attention) (15,16). However, the potential link between sensorimotor dysfunction and hallucinations and passivity symptoms is sparsely studied in 22q11DS. Only a few studies examined the linear relationship between deficits in self-monitoring and hallucinations (or symptoms dimensions of positive schizotypy) in 22q11DS, showing that adolescents with the microdeletion exhibit source monitoring impairment when performing an action monitoring paradigm and a speech-monitoring task (17,18). The pattern of results corresponds to what is observed in patients with schizophrenia, but the authors did not find any significant correlations between deficits in self-monitoring and schizotypal symptoms (e.g., thought disorders, unusual perceptual experiences, which are similar to passivity symptoms).

On the neural level, 22q11DS individuals present abnormal structural and functional connectivity, which can be indicative of an early expression of prodromal or clear psychotic symptoms. Studies mostly show alterations in resting state (rs) functional connectivity in the default mode network (DMN), namely a reduction of connectivity between the anterior and posterior cingulate cortex (ACC and PCC) and the left superior frontal gyrus region (19,20). Altered connectivity to ACC was linked to the presence of psychotic symptoms (21,22). Taken together, the aforementioned findings are in line with those obtained in patients with the schizophrenia spectrum showing passivity symptoms, deficits in self-monitoring and in structural and functional connectivity (23–26). However, the link between sensorimotor prediction and occurrence of psychotic symptoms in 22q11DS has not been addressed experimentally.

Recently, we have designed a non-invasive experimental paradigm during which we safely induced, through a robotic device generating sensorimotor conflicts, a specific hallucination - the presence hallucination (PH) - in healthy and clinical populations (27–29). PH is the sensation that another person is nearby when no one is actually present and is frequently observed in epilepsy, Parkinson's disease and schizophrenia (30,31). PH is suggested to be associated to passivity symptoms of schizophrenia (32) and we demonstrated that its study is feasible with the experimental settings we designed. Through our studies, we showed that it is possible to create disturbances in self- or source monitoring and sensorimotor integration of own bodily signals to induce PH and associated passivity experiences (PE) such as LoA. Moreover, we recently defined a PH-network comprising mainly fronto-temporal areas bilaterally (i.e., posterior middle temporal gyrus (pMTG), inferior frontal gyrus (IFG) and the ventral premotor cortex (vPMC)) obtained from the combination of brain regions from healthy subjects experiencing robot-induced PH (riPH) and a network derived from neurological patients with brain lesions causing PH (28).

To date, the occurrence of PH in 22q11DS is not documented. Do individuals with the 22q11DS have symptomatic PH? If so, through the study of PH in 22q11DS, we aim at investigating whether there is a causal link between sensorimotor integration, self-monitoring and occurrence of psychotic symptoms. First, we tested the sensitivity of 22q11DS subjects to varying degrees of robot-induced sensorimotor conflicts, and their proneness to experience riPH and related PE similar to other positive symptoms. We expected individuals with

22q11DS to show higher sensitivity to sensorimotor conflicts than healthy age-matched controls, with an early riPH occurrence due to less sensory attenuation. Second, we analyzed the rs functional connectivity of the PH-network in individuals with 22q11DS and its relationship with riPHs. We predicted reduced functional connectivity within the PH-network based on our recent study on psychotic patients with passivity symptoms showing lower functional connectivity within this network (Stripeikyte et al., *submitted*). Finally, we examined neuropsychological and psychopathological correlates of riPHs and associated PE, and within the defined PH-network. We hypothesized that impairment in executive functions modulates sensorimotor integration, and linked to decreased functional connectivity within the PH-network.

2.2.3 Methods

Participants

Twenty-six individuals with 22q11DS (9 females) and 16 age-matched healthy controls (22q11DS subjects' siblings) (10 females) took part in the study. Both groups were recruited via the Developmental Imaging and psychopathology Lab, (Department of Psychiatry, University of Geneva). Participants were between 7 to 25 years old and both groups did not differ significantly in terms of age. Control subjects did not have any history of neurological or psychiatric disorders, and were not under medication. Written informed consent was obtained either from all participants or from their parents (when minors were included). The study was approved by the Swiss Ethics Committee of Geneva (CCER, Switzerland) and conducted in accordance to the Declaration of Helsinki.
Demographic, psychiatric, neuropsychological measures as well as medication are presented in Table 1.

Psychiatric measures

All participants were assessed with the Prodromal Questionnaire (PQ-16) (33), a self-report questionnaire screening for prodromal signs of psychosis. For 22q11DS subjects only, psychotic symptoms were evaluated by means of the Structured Interview for Prodromal Syndromes (SIPS) (34), and indicated that the individuals with 22q11DS were mostly asymptomatic. Their global functioning in daily life was assessed with the Global Assessment of Functioning (GAF) scale (35). Besides, through a semi-structured interview, we also assessed the occurrence of PH (and eventually its phenomenology) in all participants. While none of the controls presented symptomatic-PH, 31% of the 22q11DS subjects reported PH at least once in their life (Table 2).

Characteristics	22q11.2 DS N = 26		Healthy Controls N = 16		Statistics t	df	p
Age (years) [mean (SD)]	14.89	(4.03)	16.62	(4.03)	1.23	28.51	0.22
Schooling (years) [mean (SD)]	8.46	(2.88)	10.62	(4.20)	1.81	23.75	0.08
Total IQ [mean (SD)]	74.34	(13.59)	111.68	(12.47)	9.09	34.03	p<0.001
Verbal IQ [mean (SD)]	80.00	(14.43)	116.81	(10.86)	9.38	38.22	p<0.001
Performance IQ [mean (SD)]	73.26	(12.27)	102.23	(11.9)	6.93	25.68	p<0.001
Clinical data							
PQ16 (Prodromal Questionnaire)							
• True items [mean (SD)]	2.19	(2.00)	1.06	(0.68)	2.64	33.31	0.01
• Distress [mean (SD)]	2.07	(2.87)	0.75	(1.06)	2.15	34.77	0.04
SIPS (Structured Interview for Prodromal Syndromes)							
TOTAL							
• P1 (Unusual thought disorder - FRS) [mean (SD)]	0.75	(1.25)	n.a	n.a			
• P2 (Suspiciousness / persecutory ideas) [mean (SD)]	1.08	(1.01)	n.a	n.a			
• P3 (Grandoise ideas) [mean (SD)]	0.04	(0.2)	n.a	n.a			
• P4 (Perceptual abnormalities/hallucinations) [mean (SD)]	1.26	(1.42)	n.a	n.a			
• P5 (Disorganized comunication) [mean (SD)]	0.30	(0.7)	n.a	n.a			
GAF (General Assessment of Functionning) [mean (SD)]	77.82	(11.55)	n.a	n.a			
Pharmagological treatment							
Neuroleptics (aripiprazole), n (%)	1	(3.85 %)	0	(0)			
Psychostimulant (methylphenidate) n (%)	9	(34.6 %)	0	(0)			
Antidepressant (selective serotonin reuptake inhibitors)	3	(11.5 %)	0	(0)			
Anxiolytics (hydroxyzine) n (%)	1	(3.85 %)	0	(0)			
Antiepileptics (levetiracetam) n (%)	1	(3.85 %)	0	(0)			
Neuropsychological scores							
Stroop Test							
• Inhibition (T-score) [mean (SD)]	0.56	(0.17)	0.64	(0.13)	1.50	37.26	0.14
Verbal fluency							
• Semantic fluency (Animals) [mean (SD)]	13.88	(4.05)	19.93	(5.35)	3.88	25.51	p<0.001
Working memory							
• Letter-Digit sequence [mean (SD)]	4.42	(0.98)	5.50	(1.41)	4.45	35.99	0.01
CPT-AX (Attention)							
• Attention (% commission errors) [mean (SD)]	58.88	(8.53)	53.06	(9.24)	2.03	29.91	0.05

Table 1: Demographic, clinical and neuropsychological data.

Symptomatic PH	22q11.2 DS subjects N = 26 (17 males + 9 females)
Occurrence (incl. PBS)	8/26 (31 %)
Emotions towards PH:	
• Negative	3/8
• Positive	1/8
• None	4/8
Sex of PH	
• Male	2/8
• Female	1/8
Place of occurrence	
• Home	7/8
• Outside home	1/8
Time of occurrence	
• Daytime	1/8
• Afternoon	3/8
• Night	1/8
• Anytime	1/8
• Unknown	2/8
Location of PH	
• Right only	0/8
• Left only	1/8
• Back	5/8
• Bilateral	1/8
• Above	1/8
• Unknown	1/8

Table 2: Phenomenology of the symptomatic PH in 22q11DS subjects

Neuropsychological evaluations

General intelligence. Depending on the age of participants, their general intelligence and reasoning abilities were examined by either the Wechsler Intelligence Scale for Children (WISC-III) (36) or the Wechsler Intelligence Scale for Adults (WAIS-III) (37).

Attention. Sustained attention and impulsivity were assessed by the Continuous Performance Test (38).

Executive functions

1. Inhibition, the ability in self-monitoring by inhibiting a behavior and resisting to interference was evaluated by the Stroop task (39).

2. Initiation and cognitive control was assessed by the semantic verbal fluency (SVF) for the Animal category, which evaluates verbal fluency by giving as many animal names as possible in 1 minute without repeating several times the same name or giving proper names. It also tests different variables of executive functions such as self-monitoring, initiation and inhibition or strategic search of information (40).

3. Working memory assessed with the letter-number sequencing from WISC III and WAIS III (36,37) consists of hearing a series of letters-numbers and reporting them back with the letters in alphabetical order and digits in ascending numerical order. This test evaluates the ability to manipulate and update information mentally.

Experiment 1: robot-induced PH and PE through sensorimotor stimulations

The experimental paradigm developed and used in our previous studies was adapted (27–29) to the present study. In practice, participants were seated, blind-folded and acoustically isolated (with white noise) (Figure 1). They were asked to manipulate a front-robot (located in front of them) with their dominant hand and to perform repetitive poking movements. The latter actuated another robot (located in the back of the participants), which replicated participants' movements and touched them on their back. The sensory feedback generated by the back-robot could either be synchronous (0ms of delay between movements and touch on the back) or asynchronous (500 ms delay) to the participant's movement. One acoustic signal (400 Hz, 100ms duration) notified the participants to start, and two sounds to stop the movements. Both conditions (i.e., synchronous (sync) and asynchronous (async)) were randomly assessed and lasted two minutes each. After running each condition, a questionnaire evaluated the subjective robot-induced bodily experiences (27) felt by subjects on a 7-point Likert scale from 0 (not at all) to 6 (very strongly): 1. Feeling of self-touch; 2. Passivity Experience; 3. Presence hallucination, 4. Loss of agency; 5. Anxiety; 6. PH in front (control question 1); and 7. Impression of having 2 bodies (control question 2).

Experiment 2: robot-induced PH and PE based on varying degrees of sensorimotor conflicts

Keeping the same setting as in Experiment 1, we further assessed how the degree of sensorimotor conflicts modulated the robot-induced PH and PE. In a first part, after every 6-poking movements (automatically counted), subjects were instructed to stop their movements and say aloud "Yes" or "No" if they experienced PH ("Did you feel as if someone was close to you, behind or next to you?") and in a second part if they experienced passivity ("Did you feel as if someone else was touching your back?"). Six delays of sensorimotor conflicts (varying from 0ms to 500ms with steps of 100ms) were tested randomly in each trial. Participants had to start the movements when they heard one auditory tone and stop when they heard 2. Each part consisted of three sessions of 18 trials (3 trials per delay).

Experiment 3: resting-state fMRI acquisition

Image acquisition. All participants were scanned with a 3T Siemens Magneton Prisma scanner using 64 head-channel. The 200 functional scans were acquired using a 8 min EPI sequence (TR=2.4 s, TE=30 ms, flip angle=85°, field of view=235 mm, slice thickness=3.2 mm, 38 slices) and the anatomical image with a T1-weighted sequence (TR=2.5 s, TE=3 ms, flip angle=8°, field of view=23.5 cm2, 192 slices).

Image preprocessing. Resting state analysis was analyzed and preprocessed using the CONN-fMRI Functional Connectivity toolbox (v.18.a) (41) and SPM12 in Matlab 2018. The standard pipeline of preprocessing was applied (i.e. slice time and motion correction, co-registration of the anatomical scan, normalization into MNI space and smoothing with a 6 mm3 FWHM Gaussian kernel) for each subject. The mean frame-wise displacement (FD) was calculated for every participant to ensure subjects did not move excessively during the resting state acquisition (all participants had a mean FD<0.25) (42). No difference in movement over the acquisition was observed between the two groups ($t(43)=1.23$, $p=0.22$ with mean FD ± SD: 22q11DS subjects=0.15 ± 0.048; Controls=0.14 ± 0.044). In addition, we extracted and regressed out of the data the individual time courses of the segmented white matter and cerebrospinal fluid, the global signal time courses as well as the six motion parameters and their first-degree derivatives. Finally, the data was filtered with a bandwidth of 0.01-0.1 Hz.

Regions of interest (ROI). Based on previous work (28), we defined a PH-network including the following ROIs: the posterior middle temporal gyrus (pMTG), the inferior frontal gyrus (IFG) and the ventral premotor cortex (vPMC) in both hemispheres. In addition, we defined two control networks: the first one consisted in shifting each region of the PH-network (conserving the same shape and same number of voxels) and the second one was composed of a visual network (including the calcarine sulcus, left thalamus, left and right middle / superior occipital gyri) (43) as done previously (Stripeikyte et al., *submitted*).

Statistical analysis

Demographic, psychiatric and neuropsychological data. The difference between 22q11DS subjects and the controls in terms of demographics and neuropsychological and psychiatric scores was assessed using independent two-sample t-tests. Since our interest was mainly on passivity symptoms, we report here and analyzed the scores obtained on the positive symptoms scale of the SIPS.

Experiment 1 and 2. Ratings of the robot-induced bodily experiences questionnaire was analyzed using linear mixed effect models and permutation test (5000 iterations) to estimate significance (lmerTest and predictmeans R package (44)) with Condition as a fixed effect and Subjects as a random factor for each question of Experiment 1. We reported permutation p values. For Experiment 2, Group (22q11DS subjects vs. controls) and Delays (6 delays: 0ms, 100ms, 200ms, 300ms, 400ms and 500ms) were considered as fixed effects, Subject as random effects. Age was added as a covariate for both experiments. PH and PE ratings were combined to create a PH/PE combined score, since both are described as manifestations of a disrupted demarcation between self and other in schizophrenia (29).

Resting-state neuroimaging. For each subject, the mean time course of each ROI was extracted and correlated (Pearson correlation) to the time course of the remaining ROIs creating a connectivity matrix of correlation values (z-transformed) of the PH-network for all possible connections for each subject. Connectivity values were extracted and analyzed using R software (https://www.R-project.org/, version 3.4.0). First, we removed the connectivity outliers (4.7% of all data points) based on 1.5 IQR from the connectivity median value for each connection. Then linear mixed model with Group (22q11 or Control) and Connections (15 connections in total for the PH-network) as fixed effects, by-subject random intercepts was

applied. Age was also included as a covariate in the analysis according to the model selection based on the Akaike information criterion (AIC). Post-hoc analysis for the between group differences was performed using two-sample t-tests (two tailed), FDR p=0.05 corrected for multiple comparisons.

Correlation analyses. The relationship between the connections showing altered functional connectivity in 22q11DS subjects compared to controls and the neuropsychological measures were investigated. We performed spearman 2-tailed correlation analysis using FDR correction for multiple comparisons. Correlations between the ratings collected from Experiment 1 were also correlated with the neuropsychological scores using the same method (FDR correction for multiple comparison for each item independently).

2.2.4 Results

Experiment 1: robot-induced PH and PE through sensorimotor stimulations

We showed a main effect of Condition for the questionnaire item loss of agency with higher ratings in the asynchronous condition for both groups ($p=0.006$) as well as a main effect of Group ($p=0.012$) with lower ratings in 22q11DS subjects than in controls. A significant interaction between Group and Condition was also observed for loss of agency ($p=0.008$) with 22q11DS individuals not presenting any difference in experiencing the loss of agency between asynchronous and synchronous conditions compared to age-matched controls in whom higher ratings were reported for the asynchronous condition (22q11DS, async-sync: $t(78)=0.19$, $p=0.99$; Controls, async-sync: $t(40)=3.38$, $p=0.0084$;) (Figure 1B, Table S1). Contrary to our predictions, we did not find any main effect of Condition, Group or interaction between Group and Condition (all $p>0.13$) for the PH/PE combined score. In addition, a main effect of Condition ($p=0.023$) was observed for the item "self-touch" with higher ratings in the synchronous condition as previously reported (27,29). Age was included as a covariate in the analysis and was found to be related to PH/PE combined score ($p<0.001$) and to loss of agency ($p=0.018$). No other main effects or interactions were significant (all $ps>0.16$) (Table S1).

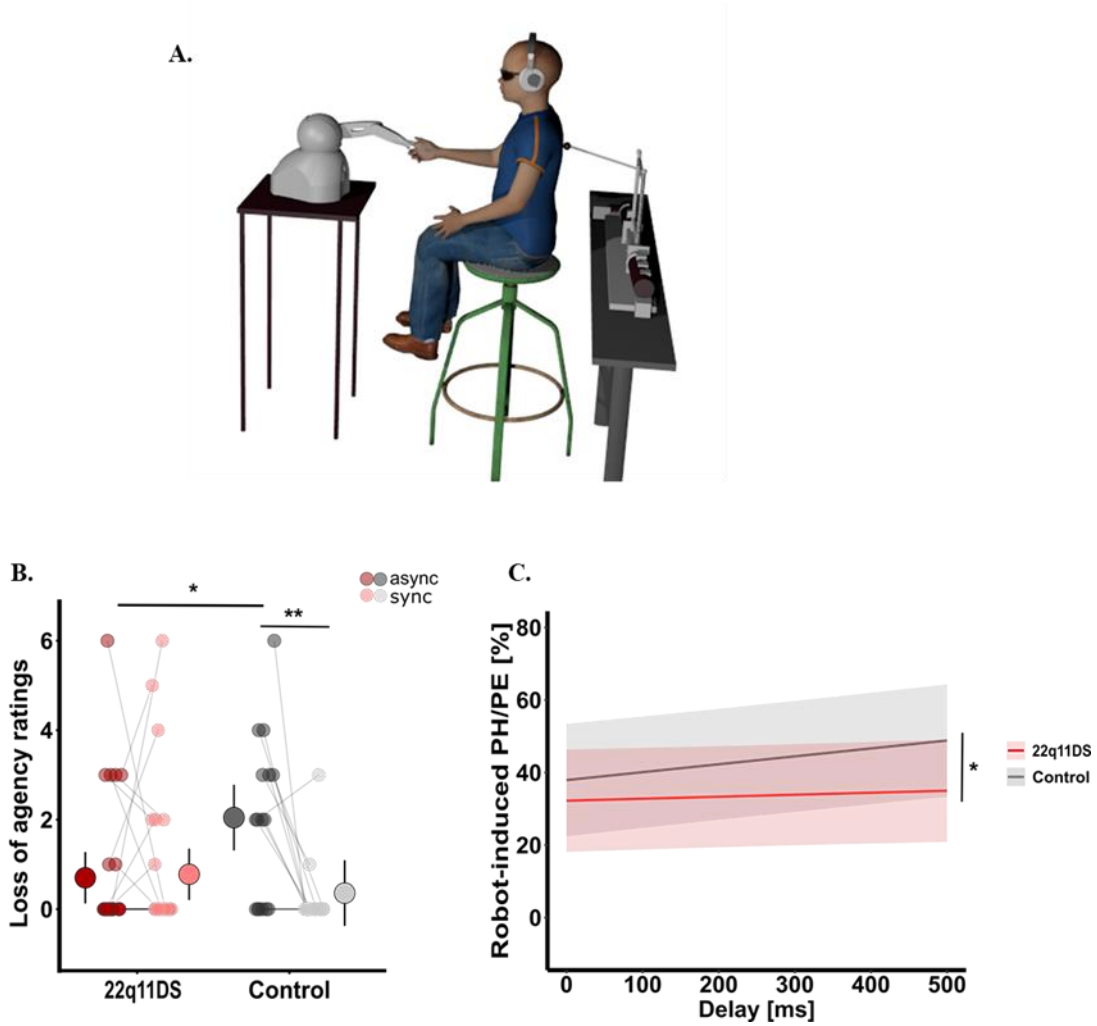

Figure 1: Experimental robotic setup and lack of sensitivity to sensorimotor stimulations. A. The robotic device consisted of a front robot, which participants will move with their right hand and a back robot that will translate the movements in the back of the participants either synchronously or asynchronously (with 500 ms delay between the movement generated in the front and the sensory feedback on the back). B. Subjects with 22q11DS did not show any difference in LoA according to the condition compared to controls where higher LoA was elicited in the asynchronous condition. C. Lack of modulation of PH/PE combined score with varying delay in subjects with 22q11DS compared to controls in which an increase of delay lead to increase PH/PE experience.

Items	Group	Conditions	Mean	SD
Self-touch	22q11 subjects	Async	1.77	2.34
Self-touch	22q11 subjects	Sync	2.15	2.09
Self-touch	Controls	Async	1.19	1.52
Self-touch	Controls	Sync	1.94	1.91
Passivity experience	22q11 subjects	Async	3.15	2.44
Passivity experience	22q11 subjects	Sync	2.58	2.35
Passivity experience	Controls	Async	3.19	2.26
Passivity experience	Controls	Sync	2.94	2.17
Presence hallucination	22q11 subjects	Async	1.50	2.06
Presence hallucination	22q11 subjects	Sync	1.04	1.59
Presence hallucination	Controls	Async	2.06	1.81
Presence hallucination	Controls	Sync	1.19	2.01
Loss of agency	22q11 subjects	Async	0.77	1.53
Loss of agency	22q11 subjects	Sync	0.85	1.69
Loss of agency	Controls	Async	1.94	1.84
Loss of agency	Controls	Sync	0.25	0.77
Anxiety	22q11 subjects	Async	0.19	0.49
Anxiety	22q11 subjects	Sync	0.12	0.43
Anxiety	Controls	Async	0.50	1.10
Anxiety	Controls	Sync	0.25	1.00
PH in front (Control)	22q11 subjects	Async	0.38	1.24
PH in front (Control)	22q11 subjects	Sync	0.35	1.23
PH in front (Control)	Controls	Async	0.00	0.00
PH in front (Control)	Controls	Sync	0.00	0.00
Impression of twow bodies (Control)	22q11 subjects	Async	0.65	1.67
Impression of twow bodies (Control)	22q11 subjects	Sync	0.88	2.01
Impression of twow bodies (Control)	Controls	Async	0.13	0.50
Impression of twow bodies (Control)	Controls	Sync	0.06	0.25

Table 3: Mean ratings and standard deviations of questionnaire items of the robot task for both groups and conditions

Experiment 2: robot-induced PH and PE based on varying degrees of sensorimotor conflicts

For this part, only 18 22q11DS subjects and 15 controls completed the task. A main effect of Delay (p=0.0020), of Group (p=0.039) and Age (p=0.001) were observed. An interaction between Group and Delay (p=0.022) was also found (Figure 1C), in which 22q11DS individuals did not show any modulation in their responses for PH/PE with respect to the delay compared to the controls in whom higher delays induced higher PH/PE experience.

Experiment 3: resting-state fMRI acquisition

Functional connectivity within PH-network showed a significant main effect of Group ($F(1,19)=5.10$, $p=0.036$) where 22q11DS subjects had a lower functional connectivity within this network which was not found in the controls networks (22q11DS, Mean=0.21; SD=0.27; Controls, Mean=0.26, SD=0.27). We also observed a significant main effect of connections ($F(14,530)=31.74$, $p<0.001$) and an interaction between the connections and the Groups ($F(14,530)=3.92$, $p<0.001$). Post-hoc analyses revealed a difference between 22q11DS subjects and controls for the bilateral pMTG connection, the right pMTG and right IFG, as well as right pMTG and right vPMC (Figure 2 and Table 4). For all connections, the functional connectivity was more reduced in 22q11DS subjects than in controls. This was not observed for the two control networks (shifted control network and standard visual network) where no significant main effect of Group nor interaction between the Connections and Group were found (all ps>0.18).

Correlations with clinical and neuropsychological scores

Functional connectivity. When correlating the neuropsychological scores specific to executive functions (SVF, working memory, inhibition and attention), we only found a significant positive correlation between the functional connectivity between the right pMTG and the right IFG and the SVF scores (FDR corrected $p=0.0018$, $R=0.57$) where higher functional connectivity was associated with higher score in verbal fluency independently of the groups (Figure 3). No other correlation was found significant with clinical scores in the 22q11DS group.

Ratings from robot-induced bodily experiences. We neither find significant correlations between the scores of the robot-induced subjective experiences and the neuroimaging data, nor with neuropsychological (all ps>0.05).

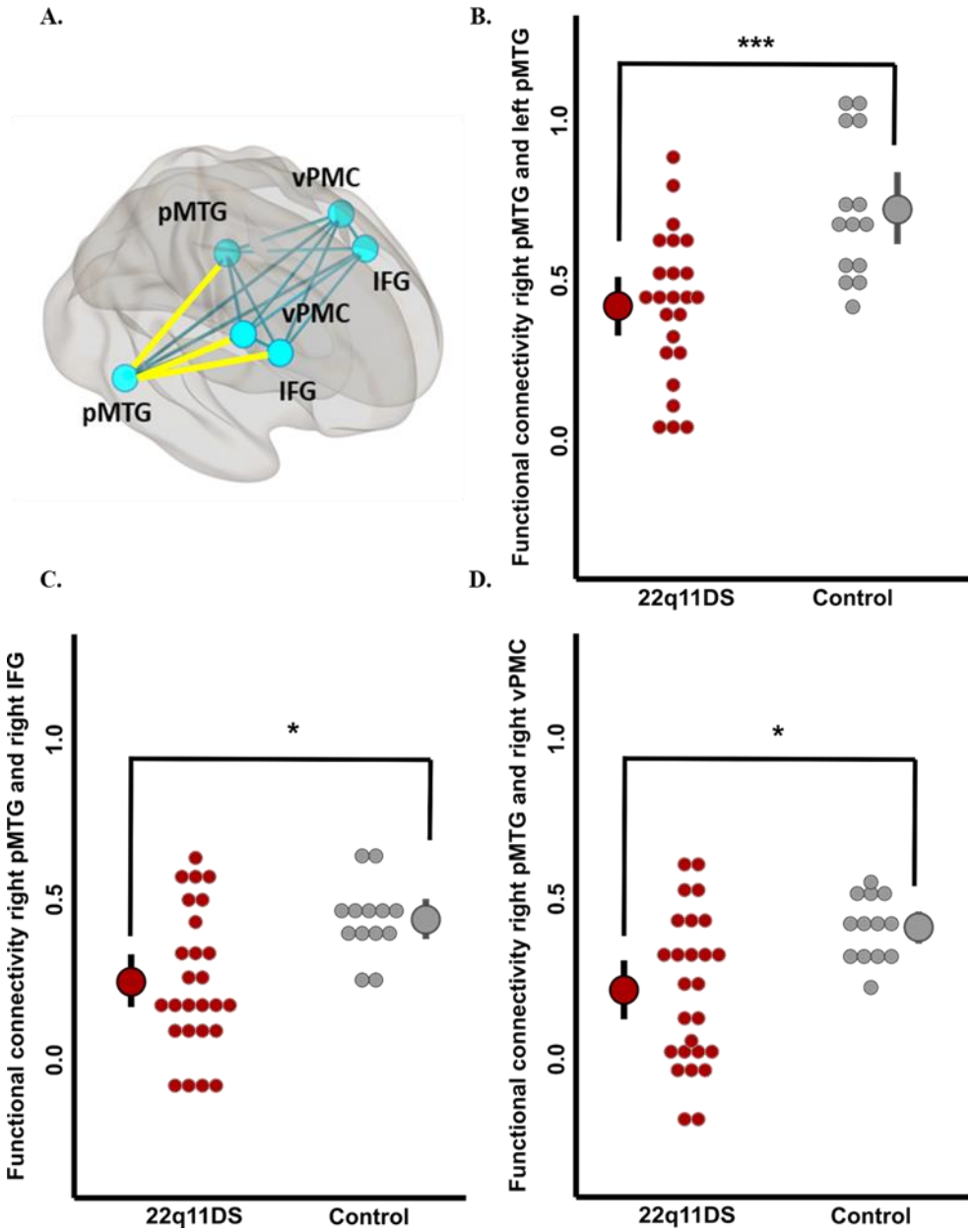

Figure 2: Functional connectivity within the PH-network. A. Connections within the PH-network that were significantly different in subjects with 22q11DS compared to age-matched controls. Reduced functional connectivity was observed in subjects with 22q11DS compared to controls between the bilateral pMTG (B), the right pMTG and right IFG (C) and the right pMTG and the right vPMC (D). ***: $p < 0.001$, *: $p < 0.05$.

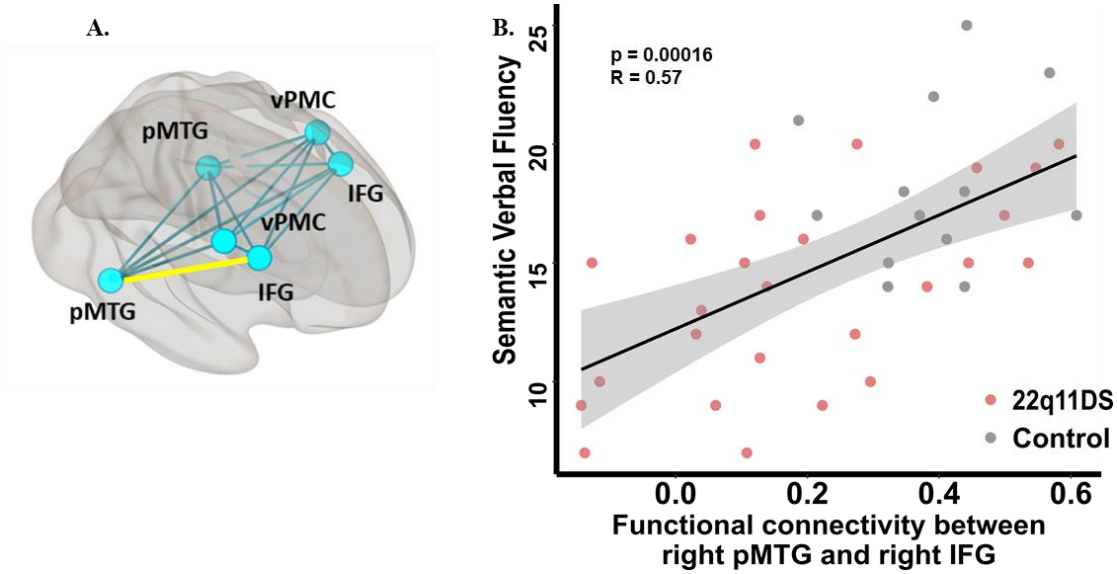

Figure 3: Correlations between the right pMTG and right IFG (A) and the semantic verbal fluency (B). Reduced functional connectivity was found between the right IFG and the right pMTG for the 22q11DS subjects compared to controls. The connectivity between those two regions further correlated with the semantic verbal fluency performance with lower connectivity associated to lower performance.

	22q11.2 DS N = 26		Healthy Controls N = 16		Statistics		
Functional connectivity	**Mean**	**SD**	**Mean**	**SD**	**t**	**df**	**p-value FDR corrected**
Right pMTG - right IFG	0.19	0.22	0.38	0.12	3.07	142.00	0.01
Right pMTG - right vPMC	0.17	0.24	0.36	0.1	3.18	123.00	0.01
Right pMTG - left pMTG	0.37	0.23	0.67	0.22	4.60	142.00	p<0.001

Table 4: Significant functional connectivity within the PH-network.

2.2.5 Discussion

PH was assessed for the first time in the present study in 22q11DS individuals, a genetic disorder associated with very high risk of developing schizophrenia. PH is a specific hallucination and has been proposed to be linked to disturbed sensorimotor integration of own body signals (27,28). Here, we report that actually 31% of individuals with 22q11DS included in our study experienced symptomatic PH at least once.

Through our robot-based experimental paradigm, we tested the sensitivity of 22q11DS individuals to sensorimotor conflicts and their proneness to experience riPH in a controlled setting. Contrary to our hypothesis, 22q11DS individuals did not present increased sensitivity to the robotic stimulations. They did not experience stronger riPH and associated PE, even when varying degrees of spatio-temporal mismatch were applied. We also observed that their sense of agency was not further disturbed by the sensorimotor stimulation compared to controls whose sense of agency was affected by the asynchronous stimulation.

On the neural level, as expected, the results revealed reduced functional connectivity within the PH-network in 22q11DS subjects compared to controls, mainly between the right pMTG and right IFG, right pMTG and right vPMC and bilateral pMTG. Although the 22q11DS subjects were asymptomatic for psychotic symptoms, especially positive ones, these findings are in line with previous work showing reduced connectivity between the right IFG and right pMTG in psychotic patients with vs. without PE (Stripeikyte et al., *submitted*). The same connection on the left hemisphere was found reduced in Parkinson's patients with PH compared to those without (28). Those findings are in favor of the fronto-temporal disconnection (supported by the forward model) described in schizophrenia (9–11).

Taken together, our results could be explained by an altered sensorimotor integration and prediction in the 22q11DS group. According to the forward model, the initiation of a motor command generates an efference copy to predict or anticipate the sensory consequences of one's action. When the prediction matches the actual sensory feedback, the action is considered as self-generated, and its perception is considered normal. However, when a mismatch between the expected outcome and the actual sensory feedback occurs, the sensory signals are less attenuated and the event is considered as originating from an external

source and not as self-generated. In 22q11DS, the lack of sensitivity to sensorimotor conflicts could indicate source monitoring confusions (18) or rapid (early) sensory attenuation of signals in these individuals. A recent study showed that 22q11DS subjects exhibit preserved prediction but rather reduced adaptations in response to repeated auditory stimuli (45). In that case, we could speculate that altered repetition suppression (i.e., reduced neural response to repeated stimuli) may cause inaccurate sensory predictions and inability to monitor and adapt to stimulus conflict. Maladaptive conflict monitoring in 22q11DS has been linked to executive dysfunctions, namely deficits in inhibition and cognitive control (46).

Interestingly, the interpretation of our results could be supported, though indirectly, by the reduced functional connectivity between the right IFG and right pMTG which is positively correlated with the SVF task. Besides assessing language abilities, the SVF task also involves executive functions such as self-monitoring, cognitive control and initiation/inhibition abilities (47). In 22q11DS subjects, an atypical developmental trajectory was observed for the SVF task, and this was not explained by poor lexical level, but most likely due to executive dysfunctions (48). Proposed as a potential marker of psychosis (49), low SVF performance is also associated with reduced activity in the right IFG and bilateral temporal cortex in high-risk for psychosis adolescents (50). Based on these findings, it is likely possible that deficits in self-monitoring and cognitive control affect sensitivity of 22q11DS individuals to sensorimotor conflicts.

Our study has a few limitations to consider. The absence of direct correlations between ratings from the robot task with both functional connectivity and executive dysfunctions makes it difficult to unravel the underlying mechanisms of PH and related PE in 22q11DS. Although 31% of 22q11DS individuals had symptomatic PH, it was not possible to directly compare subjects with vs. without PH, nor were we able to stratify and compare the group of 22q11DS according to the presence of attenuated positive symptoms since most individuals were asymptomatic. Future studies with larger cohorts could overcome this selection bias and determine whether PH would precede marked positive symptoms, and give insight on the behavioral and neural mechanisms.

Using a robot-based experimental paradigm, we found a lack of sensorimotor modulation in individuals with 22q11DS asymptomatic for psychosis, but presenting executive dysfunctions and reduced fronto-temporal connectivity compared to age-matched controls. Deficits in

cognitive control and self-monitoring could be further studied to determine whether they could represent possible markers for specific psychotic symptoms such as passivity symptoms before their onset. To conclude, it would also be of clinical relevance to better characterize the phenomenological aspects of PH and related PE in a larger sample of individuals with 22q11DS.

2.2.6 References

1. Fomin AB, Pastorino AC, Kim CA, Pereira AC, Carneiro-Sampaio M, Abe Jacob CM. DiGeorge Syndrome: a not so rare disease. Clinics (Sao Paulo). 2010 Sep;65(9):865–869.
2. McDonald-McGinn DM, Sullivan KE, Marino B, Philip N, Swillen A, Vorstman JAS, et al. 22Q11.2 Deletion Syndrome. Nature Reviews Disease Primers. 2015;1(November).
3. Debbané M, Glaser B, David MK, Feinstein C, Eliez S. Psychotic symptoms in children and adolescents with 22q11.2 deletion syndrome: Neuropsychological and behavioral implications. Schizophr Res. 2006 Jun;84(2–3):187–193.
4. Schneider M, Schaer M, Mutlu AK, Menghetti S, Glaser B, Debbané M, et al. Clinical and cognitive risk factors for psychotic symptoms in 22q11.2 deletion syndrome: a transversal and longitudinal approach. Eur Child Adolesc Psychiatry. 2014 Jun;23(6):425–436.
5. Chow EWC, Zipursky RB, Mikulis DJ, Bassett AS. Structural Brain Abnormalities in Patients with Schizophrenia and 22q11 Deletion Syndrome. Biol Psychiatry. 2002 Feb 1;51(3):208–15.
6. Bassett AS, Chow EWC. Schizophrenia and 22q11.2 Deletion Syndrome. Curr Psychiatry Rep. 2008 Apr;10(2):148–157.
7. Schneider M, Debbané M, Bassett AS, Chow EWC, Fung WLA, van den Bree M, et al. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. Am J Psychiatry. 2014 Jun;171(6):627–639.
8. Kook SD, An SK, Kim KR, Kim WJ, Lee E, Namkoong K. Psychotic Features as the First Manifestation of 22q11.2 Deletion Syndrome. Psychiatry Investig. 2010 Mar;7(1):72–4.
9. Friston K, Brown HR, Siemerkus J, Stephan KE. The dysconnection hypothesis (2016). Schizophrenia Research. 2016 Oct;176(2):83–94.
10. Frith C. Explaining the symptoms of schizophrenia: Abnormalities in the awareness of action. Brain Research Reviews. 2000 Mar;31(2–3):357–63.
11. Kendler KS, Mishara A. The Prehistory of Schneider's First-Rank Symptoms: Texts From 1810 to 1932. Schizophr Bull. 2019 11;45(5):971–90.
12. Blakemore SJ, Smith J, Steel R, Johnstone CE, Frith CD. The perception of self-produced sensory stimuli in patients with auditory hallucinations and passivity experiences: evidence for a breakdown in self-monitoring. Psychol Med. 2000 Sep;30(5):1131–9.
13. Graham-Schmidt KT, Martin-Iverson MT, Waters FAV. Self- and other-agency in people with passivity (first rank) symptoms in schizophrenia. Schizophr Res. 2018;192:75–81.
14. Werner J-D, Trapp K, Wüstenberg T, Voss M. Self-attribution bias during continuous action-effect monitoring in patients with schizophrenia. Schizophrenia Research. 2014 Jan;152(1):33–40.
15. Sobin C, Kiley-Brabeck K, Karayiorgou M. Lower Prepulse Inhibition in Children With the 22q11 Deletion Syndrome. Am J Psychiatry. 2005 Jun;162(6):1090–1099.
16. Cunningham AC, Hill L, Mon-Williams M, Peall KJ, Linden DEJ, Hall J, et al. Using kinematic analyses to explore sensorimotor control impairments in children with 22q11.2 deletion syndrome. J Neurodev Disord. 2019 Jun;11(1):8.
17. Debbané M, Van Der Linden M, Glaser B, Debbane M, Eliez S. Monitoring of self-generated speech in adolescents with 22q11 . 2 deletion syndrome. British Journal of clinical psychology. 2010;49:373–86.

18. Debbané M, Linden MV der, Glaser B, Eliez S. Source monitoring for actions in adolescents with 22q11.2 deletion syndrome (22q11DS). Psychological Medicine. 2008 Jun;38(6):811–20.
19. Padula MC, Schaer M, Scariati E, Schneider M, Van De Ville D, Debbané M, et al. Structural and functional connectivity in the default mode network in 22q11.2 deletion syndrome. J Neurodev Disord. 2015 [cited 2020 Feb 28];7(1).
20. Debbané M, Lazouret M, Lagioia A, Schneider M, Van De Ville D, Eliez S. Resting-state networks in adolescents with 22q11.2 deletion syndrome: associations with prodromal symptoms and executive functions. Schizophr Res. 2012 Aug;139(1–3):33–39.
21. Scariati E, Schaer M, Richiardi J, Schneider M, Debbané M, Van De Ville D, et al. Identifying 22q11.2 deletion syndrome and psychosis using resting-state connectivity patterns. Brain Topogr. 2014 Nov;27(6):808–821.
22. Zöller D, Schaer M, Scariati E, Padula MC, Eliez S, van de Ville D. Disentangling resting-state BOLD variability and PCC functional connectivity in 22q11.2 deletion syndrome. NeuroImage. 2017;149:85–97.
23. Carter CS, MacDonald AW, Ross LL, Stenger VA. Anterior Cingulate Cortex Activity and Impaired Self-Monitoring of Performance in Patients With Schizophrenia: An Event-Related fMRI Study. AJP. 2001 Sep 1;158(9):1423–8.
24. Crossley NA, Mechelli A, Fusar-Poli P, Broome MR, Matthiasson P, Johns LC, et al. Superior temporal lobe dysfunction and frontotemporal dysconnectivity in subjects at risk of psychosis and in first-episode psychosis. Human Brain Mapping. 2009;30(12):4129–37.
25. Karbasforoushan H, Woodward ND. Resting-state networks in schizophrenia. Curr Top Med Chem. 2012;12(21):2404–14.
26. Kumari V, Fannon D, Ffytche DH, Raveendran V, Antonova E, Premkumar P, et al. Functional MRI of Verbal Self-monitoring in Schizophrenia: Performance and Illness-Specific Effects. Schizophr Bull. 2010 Jul 1;36(4):740–55.
27. Blanke O, Pozeg P, Hara M, Heydrich L, Serino A. Neurological and Robot - Controlled Induction of an Apparition. Current Biology. 2014;24.
28. Bernasconi F, Blondiaux E, Potheegadoo J, Stripeikyte G, Pagonabarraga J, Bejr-Kasem H, et al. Sensorimotor hallucinations in Parkinson's disease. Neuroscience; 2020.
29. Salomon R, Progin P, Griffa A, Rognini G, Do KQ, Conus P, et al. Sensorimotor Induction of Auditory Misattribution in Early Psychosis. Schizophrenia Bulletin. 2020 Feb 11;sbz136.
30. Arzy S, Seeck M, Ortigue S, Spinelli L, Blanke O. Induction of an illusory shadow person. Nature. 2006 Sep 21;443(7109):287.
31. Llorca PM, Pereira B, Jardri R, Chereau-Boudet I, Brousse G, Misdrahi D, et al. Hallucinations in schizophrenia and Parkinson's disease: an analysis of sensory modalities involved and the repercussion on patients. Sci Rep. 2016 Dec 1;6(1):1–9.
32. Jaspers K. Über leibhaftige Bewußtheiten (Bewußtheitstäuschungen), ein psychopathologisches Elementarsymptom. In: Jaspers K, editor. Gesammelte Schriften zur Psychopathologie. Berlin, Heidelberg: Springer Berlin Heidelberg; 1913 [cited 2019 Jan 23]. p. 413–20.
33. Ising HK, Veling W, Loewy RL, Rietveld MW, Rietdijk J, Dragt S, et al. The Validity of the 16-Item Version of the Prodromal Questionnaire (PQ-16) to Screen for Ultra High Risk of Developing Psychosis in the General Help-Seeking Population. Schizophr Bull. 2012 Nov;38(6):1288–96.

34. Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophr Bull. 2003;29(4):703–715.
35. Endicott J, Spitzer RL, Fleiss JL, Cohen J. The Global Assessment Scale: A Procedure for Measuring Overall Severity of Psychiatric Disturbance. Arch Gen Psychiatry. 1976 Jun 1;33(6):766–71.
36. Wechsler D. The Wechsler intelligence scale for children—third edition: administration and scoring manual. Psychological corporation. San Antonio; 1991.
37. Wechsler D. Wechsler adult intelligence scale-III: administration and scoring manual. Psychological Corporation. San Antonio; 1997.
38. Conners CK, Staff MHS. Conner's continuous performance test II: computer program for windows technical guide and software manual. Multi-Health Systems. North Tonawanda; 2000.
39. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol. 1935;643–62.
40. Cardebat D, Démonet JF, Viallard G, Faure S, Puel M, Celsis P. Brain Functional Profiles in Formal and Semantic Fluency Tasks: A SPECT Study in Normals. Brain and Language. 1996 Feb;52(2):305–313.
41. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: A Functional Connectivity Toolbox for Correlated and Anticorrelated Brain Networks. Brain Connectivity. 2012;2(3):125–141.
42. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. NeuroImage. 2012;59(3):2142–2154.
43. Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD. Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cerebral Cortex. 2012;22(1):158–65.
44. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest Package: Tests in Linear Mixed Effects Models . Journal of Statistical Software. 2017;82(13).
45. Larsen KM, Mørup M, Birknow MR, Fischer E, Olsen L, Didriksen M, et al. Individuals with 22q11.2 deletion syndrome show intact prediction but reduced adaptation in responses to repeated sounds: Evidence from Bayesian mapping. Neuroimage Clin.
46. Bish JP, Ferrante SM, McDonald-McGinn D, Zackai E, Simon TJ. Maladaptive conflict monitoring as evidence for executive dysfunction in children with chromosome 22q11.2 deletion syndrome. Developmental Science. 2005;8(1):36–43.
47. Whitney C, Kirk M, O'Sullivan J, Lambon Ralph MA, Jefferies E. The Neural Organization of Semantic Control: TMS Evidence for a Distributed Network in Left Inferior Frontal and Posterior Middle Temporal Gyrus. Cereb Cortex. 2011 May 1;21(5):1066–75.
48. Maeder J, Schneider M, Bostelmann M, Debbané M, Glaser B, Menghetti S, et al. Developmental trajectories of executive functions in 22q11.2 deletion syndrome. J Neurodev Disord. 2016;8:10–10.
49. Becker HE, Nieman DH, Dingemans PM, Fliert JR [van de, Haan L [De, Linszen DH. Verbal fluency as a possible predictor for psychosis. European Psychiatry. 2010;25(2):105–10.
50. Jacobson S, Kelleher I, Harley M, Murtagh A, Clarke M, Blanchard M, et al. Structural and functional brain correlates of subclinical psychotic symptoms in 11–13 year old schoolchildren. NeuroImage. 2010;49(2):1875–85.

PART II

The major work has been done to show that self-monitoring involves prediction mechanisms that allow to distinguish between self and externally generated stimuli. Predicting whether the stimuli is self-generated is crucial for a coherent orientation in the environment and the sense of agency. It also helps to save processing resources and ensure smooth performance, thus self-generated stimuli are perceived as less salient, or in other words they are attenuated compared to the same external stimuli. This is well documented in the motor tasks such as sound generation or arm movement. However, it is not showed yet whether this attenuation of self-generated stimuli also applies to higher-level cognitive functions beyond sensorimotor processes. Patients with psychotic symptoms such as thought insertion, where one's own thoughts are misperceived as generated by someone else raises the suggestion that there are specific mechanisms accounting for self-other distinction during higher-level cognitive processes such as thoughts. Therefore, Study 3, investigated if attenuation of self-generated stimuli applies to higher-level cognitive processes such as numerosity estimations and what neural mechanisms are related to this. In Study 4, this work was extended to psychotic patients with thought insertion, to investigate whether this self-attenuation during higher-level cognitive task is affected in the patients and linked to the neural mechanisms accounting for an alien entity (PH-network). These two studies contribute to the scientific field by showing that indeed higher-level cognitive processing beyond sensorimotor involvement is a subject of self-attenuation. We suggest that attenuation during self-generated numerosity estimations could be ensured by an increased functional connectivity between IPS, the key numerosity area and extended network which is related to the attenuation processes more generally (Study 3). Further, in Study 4 we show that cognitive self-attenuation is not distinct between healthy controls and psychotic patients with thought insertion. Yet, it has a more complex relation with altered executive functioning in psychotic patients with thought insertion. Lastly, we found that psychotic patients with thought insertion had altered functional connectivity within the network accounting for the alien entity (PH-network) and that one of the affected connections was related to the varying levels of cognitive self-attenuation.

3.1 STUDY 3: COGNITIVE SELF-ATTENUATION DURING WORD NUMEROSITY ESTIMATIONS

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Author Contributions
GS, NF, GR, OB developed the study concept and contributed to the study design. Testing, data collection and data analysis were performed by GS. GS, NF, MP, and OB drafted the paper; all authors provided critical revisions and approved the final version of the paper for submission.
The authors declare no competing interests.

3.1.1 Abstract

Previous studies have shown that self-generated stimuli in auditory, visual, and somatosensory domains are attenuated, producing decreased behavioral and neural responses compared to the same stimuli that are externally generated. Yet, whether such attenuation also occurs for higher-level cognitive functions beyond sensorimotor processing remains unknown. In this study, we assessed whether cognitive functions such as numerosity estimation are subject to attenuation. We designed a task allowing the controlled comparison of numerosity estimations for self (active condition) and externally (passive condition) generated words. Our behavioral results showed a larger underestimation of self compared to externally-generated words, suggesting that numerosity estimates for self-generated words are attenuated. Plus, the linear relationship between the reported and actual number of words was stronger for self-generated words, although the ability to track errors about numerosity estimations was similar across conditions. Neuroimaging results revealed that numerosity underestimation involved increased functional connectivity between the right intraparietal sulcus and an extended network (bilateral supplementary motor area, left inferior parietal lobule and left superior temporal gyrus) when estimating the number of self vs externally generated words. We interpret our results in light of two models of attenuation, and discuss whether they stem from perceptual versus cognitive origins.

3.1.2 Introduction

The ability to distinguish self- versus externally-generated stimuli is crucial for self-representation (1,2). A typical distinction between stimuli generated by oneself and those caused by external sources involves self-attenuation, whereby self-generated stimuli are perceived as less intense. Indeed, previous studies have shown that self-produced overt stimuli, in auditory (3,4), visual (5,6) and somatosensory domains (7,8), are attenuated compared to the same stimuli when they are externally generated. This attenuation was shown at the behavioral, as well as at the neural level, both in sensory (e.g., auditory cortex (9)) and supramodal brain areas such as thalamus, cerebellum, inferior parietal cortex (10,11). Previous studies have shown that such self-attenuation effects extend beyond overt actions, and notably apply to motor imagery (12) or inner speech (13–16). In the latter case, attenuation of the electrophysiological (14,15) and behavioral (17) response corresponding to the test phoneme was observed when it matched the imagined cued phoneme compared to the passive listening or mismatch between heard and imagined phonemes. These studies used phonemes that are integrated into the early stages of hierarchical speech processing (18,19) which involve low-level sensory cortices (20,21), where self-attenuation effects have been repeatedly demonstrated (22). An outstanding question is whether self-attenuation is limited to sensory representations or extends to non-sensory higher-level cognitive processes.

To answer this question, we investigated the cognitive function of numerosity estimations, defined as approximate judgments when counting is not involved (23). The properties of numerosity estimations such as its a-modality, it being innate or its precision linearly decreasing with increasing numerosity have been well described (24,25). Extensive neuroimaging work has established that the intraparietal sulcus (IPS) plays a key role in numerosity processing (for review see: 25). If self-attenuation extends to non-sensory cognitive processes, we might expect attenuated IPS activity when estimating the number of items that where self-generated compared to externally-generated. Thus, this study aimed at investigating whether numerosity estimations of self-generated words were attenuated compared to numerosity estimations of heard words, thereby demonstrating that self-attenuation applies to non-sensory cognitive processes. Second, we sought to show which brain regions and networks showed hemodynamic activity related to attenuation processes.

For this, we designed a paradigm allowing the comparison of numerosity estimations of either self-generated words (active condition) or externally-generated words (passive condition) while recording concurrent brain activity through functional magnetic resonance imaging (fMRI). In the active condition, words were covertly generated while participants performed a phonetic verbal fluency task, where they had to produce the words starting with a given cue letter. Conversely, in the passive condition, participants listened to a stream of pre-recorded words (externally-generated). Importantly, after both (active, passive) conditions, participants were asked how many words they had generated or heard (numerosity estimation), followed by an evaluation of the error they could have made in their estimation (performance monitoring). Assuming that self-attenuation is occurring during numerosity estimations (active condition), we predicted that participants would underestimate the number of self- vs. externally-generated words and explored possible effects on performance monitoring. At the neural level, considering that self-attenuation extends to non-sensory processes, we expected to find reduced BOLD signal during the active vs. passive condition not only in brain regions involved in speech processing like shown before (27–29), but also in those responsible for numerosity processing including the IPS.

3.1.3 Methods

Participants

Two independent participant groups were tested in this study. First, we performed a behavioral pilot experiment in the mock scanner, where we tested 17 (6 women) participants; the age range was 18 – 28 years (M = 23 years, CI(95%) = [23, 24]); schooling level varied between 13 and 21 years (M = 17 years, CI(95%) = [16, 18]). During the main fMRI experiment, we studied 25 (14 women) participants; the age range was 18 – 37 years (M = 23 years, CI(95%) = [22, 26]). Schooling level varied from 12 to 22 years (M = 17 years, CI(95%) = [16, 18]). All participants were right-handed determined using the Edinburgh Hand Preference Inventory (30) and native French-speaking healthy volunteers with no history of neurological or psychiatric disease and no recent reported history of drug use. Participants had normal or corrected-to-normal vision and no claustrophobia. All participants were naive to the purpose of the study, gave informed consent in accordance with institutional guidelines and the Declaration of Helsinki, and received monetary compensation (20 CHF / hour). The study was approved by the local ethical committee of the canton Geneva (ID: 2015-00092).

Experimental task

The experiment was performed in the mock scanner environment (both for the behavioral pilot experiment and the training for the main fMRI experiment) and in the MRI scanner (main fMRI experiment). The experiment contained phonetic verbal fluency and passive word listening tasks, followed by numerosity and error estimations (Figure 1). The task consisted of two conditions (20 trials each) during which participants either covertly generated words (active condition) or listened to pre-recorded words (passive condition). Each trial started with a randomly jittered inter-trial interval varying between 4 s and 4.75 s, followed by an audio cue (2 s) indicating which condition will follow and a recorded cue letter (2 s). Next, the word generation phase lasted between 20 s and 35 s; in the active condition, it consisted of a phonetic verbal fluency task, in which participants had to covertly generate words starting with a cued letter (Figure 1, top). For each generated word, participants were asked to press a response button. In the passive condition, a series of pre-recorded audio words were played to the participants. Participants were asked to press the response button for every word that contained the cue letter (Figure 1, bottom). In both conditions, the end of the generation/listening phase was indicated by an audio cue (0.5 s). After that, participants first

reported the estimation of total number of words generated (active condition) or heard (passive condition). For this, they used two buttons that moved a slider displayed on the screen. The slider was presented as a random integer (ranging from 0 to 20) which could be changed in value by pressing the response box buttons (left button – decrease the value, right button – increase the value). This was followed by the error estimation, where participants were asked to evaluate their performance on the numerosity estimation by estimating the magnitude of the error they thought they may have made (in number of words). For this, an automatically sliding bar was presented, and the participant had to select with one button press the desired value (e.g., +/- 2 words error). Values varied from +/- 0 words (e.g., numerosity response judged as correct) to +/- 5 words mistaken. The total time for numerosity and error estimations were restricted to a maximum of 7 s. Except for this responding time, participants were asked to perform the task with eyes closed.

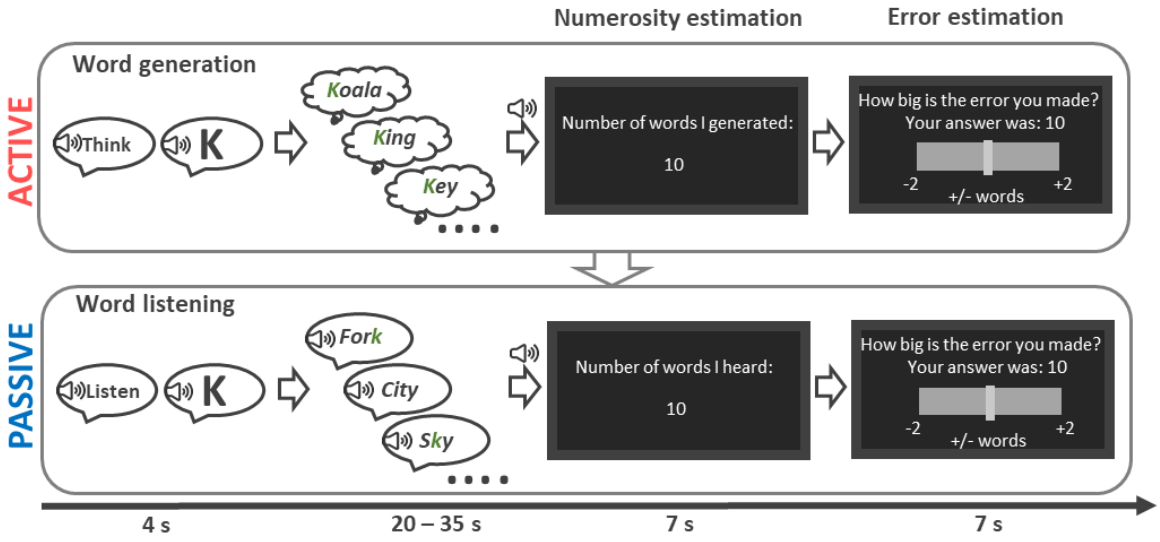

Figure 1. Schematic representation of the general task flow: active (top) and passive (bottom) conditions consisting of instruction, word generation/listening, numerosity and error estimation parts. Each condition was repeated 4 times per block. Auditory and visual instructions were provided in French.

Stimuli

All stimuli were prepared and presented using Matlab 2016b (mathworks.com) and the Psychtoolbox-3 toolbox (psychtoolbox.org; (31–33)). Twenty different cue letters were used for the active and passive conditions. The same cue letter was used once during the active and once during the passive condition in the counterbalanced order. Played back words during the passive condition were chosen from a list of 420 French words (34). The audio

stimuli presented during the task were recorded by male and female native French speakers in a neutral manner and registered in wav format with 11025Hz sampling frequency. The gender of the voice pronouncing words in the passive condition was matched to the participants' gender. During the experiment, participants were equipped with MRI compatible earphones, and report buttons for the right hand.

Procedure

Participants were trained in a mock scanner prior to the main fMRI experiment in order to familiarize themselves with the task. They were asked to perform four trials of the task during the training (twice for each condition), with the cue letters 'j' and 'k'. These letters were not used later during the main fMRI experiment.

The experiment consisted of three runs lasting approximately 15 min each with short breaks in-between. The total duration of a trial varied between 40 and 55 s due to pseudorandomized time for word generation/ listening phase. This time variability was introduced to avoid habituation and predictability for the number of generated/heard words and to decorrelate hemodynamic activity related to word generation/listening and numerosity estimations. The experiment was designed in 10 blocks with 4 trials of the same condition per block. The blocks of the active condition trials always preceded the blocks of the passive condition, allowing us to use the number and pace of generated words that were recorded based on participant's button presses to playback the words during the next block of the passive condition. The order of the number of words played during the passive condition was shuffled within the block. This was done to ensure that participants are not able to recognize whether the number and pace of the played words are matching their generation of the preceding active condition block.

After the main experiment, a standard phonemic verbal fluency (generation time of 60 s, cue letter 'p') test (35) was performed overtly to verify that subjects understood the task correctly. Overall, the experiment lasted approximately 1h 30 min (MRI session) and 1h in the mock scanner (pilot session). The pilot mock scanner study contained the same procedure as the main MRI experiment, except for the shorter breaks between the runs since there was no MRI scanning involved.

Behavioral performance measures

Most statistical frameworks to analyze performance monitoring have been developed for discrimination tasks with a binary response (e.g., Fleming and Lau 2014 for a review). In the following, we propose two indices of numerosity performance and performance monitoring to analyze ordinal data (e.g., number of words). In addition to the prerequisites described below, these indices were defined at the single-trial level so they could serve as parametric regressors of interest in the fMRI analysis.

The numerosity performance index is an accuracy ratio reflecting how correctly participants estimated the number of words during the generation/listening phase. For each trial, we wanted signed numerosity performance to be proportional to the difference between the reported number of generated/heard words (numerosity estimation; [N]) and the actual number of words generated/heard [W]. We normalized this difference by the sum of numerosity estimation and actually generated/heard number of words [N+W] (equation 1) to give more weight to errors made about low numbers of words (i.e., an error of +/- 2 given a numerosity estimation of 8 has higher magnitude than an error of +/-2 given a numerosity estimation of 16; Figure S1 A). Negative numerosity performance values thus reflected an underestimation of generated/heard words, and positive values reflected an overestimation of generated/heard words. In contrast, null numerosity performance values reflected correct answers about the number of generated/heard words.

$$numerosity\ performance\ = \frac{N-W}{N+W} \quad \text{(Equation 1)}$$

Performance monitoring reflected how well participants estimated an error about their previous performance. We defined it as the absolute value of the difference between the error estimation [E] and (accuracy [N-W]), normalized by the sum of the numerosity estimation and words generated/heard [N+W] (equation 2). Normalization was done in order to consider the difficulty; the same error made when estimating the low number of words or high number of words should be penalized proportionally. A performance monitoring value of 0 reflected ideal error tracking, whereby participants correctly estimated the error made during the numerosity estimation. An increase of performance monitoring value represented

an increase in error magnitude while estimating the difference between numerosity estimation and the actual number of words generated/heard (Figure S1 B, C).

$$performance\ monitoring\ = |\frac{E - |N - W|}{N + W}|$$ (Equation 2)

Trials for which participants did not generate at least 6 words or failed to answer numerosity or error estimations within the time limit were excluded from behavioral and fMRI analysis (in total 2.44 ± 1.87 trials/subject were excluded). The threshold of 5 words was selected according to the working memory capacity of ~3-5 items (37). Considering all participants' data, 6.1% of all trials were discarded.

Behavioral data analysis

All continuous variables (numerosity performance, performance monitoring) were analyzed using linear mixed-effects models with the condition ("active", "passive") as a fixed effect and a random intercept by participant and condition. The inclusion of additional random effects was guided by model comparison and selection based on Bayesian Information Criteria. Analyzes were performed using the lme4 (38) and lmerTest (39) packages in R (www.R-project.org). The significance of fixed effects was estimated using Satterthwaite's approximation for degrees of freedom of F statistics (40).

fMRI data acquisition

MRI data were acquired using a Siemens Magnetom Prisma 3 T scanner with a 64-channel head coil. T1 weighted (1 mm isotropic) scans were acquired using a Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence (TR = 2300 ms; TI = 900 ms; TE = 2.25 ms; flip-angle = 8 degrees; GRAPPA = 2; FOV = 256 × 256 mm; 208 slices). Functional scans were obtained using echo-planar (EPI) sequence (multiband acceleration = 6; TR = 1000 ms; TE = 32 ms; flip-angle = 58 degrees; FOV = 224 × 224 mm; matrix = 64 x 64; slice thickness = 2 mm; number of slices = 66). The number of functional image volumes varied according to the experiment duration (2278 ± 61 volumes).

fMRI data preprocessing

Anatomical and functional images were processed and analyzed using SPM-12 (Welcome Department of Cognitive Neurology, London, UK). Pre-processing steps included slice time correction, field-map distortion correction, realignment and unwarping to spatially correct for head motions and distortions, co-registration of structural and functional images, normalization of all images to common Montreal Neurological Institute (MNI) space, and spatial smoothing with a Gaussian kernel with a full-width at half maximum (FWHM) of 4 mm. Quality assurance of all EPI images was performed with criteria of maximum 2 mm translation and 2° rotation between volumes. In addition, an excessive movement was estimated with the mean framewise displacement (FD) (41) with the exclusion threshold of 0.5 mm. None of the participants had a higher mean FD (0.2 ± 0.06 mm) than the set threshold.

fMRI data analysis

We used a two-level random-effects analysis. In the first-level analysis, condition-specific effects were estimated according to a general linear model (GLM) fitted for each subject. An average mask of grey matter from all subjects was built using FSL (fsl.fmrib.ox.ac.uk/fsl) and used to mask out white matter and non-brain tissues. The GLM was built using six boxcar regressors corresponding to the duration of the word generation/listening phase, numerosity estimation and error estimation in the active and passive conditions. Parametric modulators of numerosity performance and performance monitoring were included in the numerosity estimation and error estimation regressors, respectively. Further, we added regressors of no interest corresponding to audio instructions, button presses and excluded trials, plus six regressors for head motion (translation and rotation).

At the second-level (group level), we performed a one-way analysis of variance (ANOVA) with F-tests to assess main effects common to active and passive conditions and t-tests to analyze the difference between the conditions (active vs. passive) for each regressor of interest: numerosity estimation and error estimation. We used a voxel-level statistical threshold of $p<0.001$ and corrected for multiple comparisons at the cluster level using family-wise error (FWE) correction with the threshold of $p<0.05$. We used the anatomical automatic labelling (AAL) atlas for brain parcellation (42).

Functional connectivity analysis

Psychophysiological Interaction (PPI) analysis was employed to identify modulations of functional coupling between a seed region and other brain regions by experimental conditions (active vs. passive) (43). To perform this analysis, we used generalized psychophysiological interaction (gPPI) toolbox version 13.1 (44). Spheres of 6 mm radius were formed around the peak coordinates of the right IPS (x = 29; y = -65; z = 50) and the left IPS (x = -27; y = -66; z = 47) clusters that were identified in the second-level analyses (see results). First-level (individual) GLM analyses were performed including task regressors of numerosity estimation or error estimation (psychological term) and time course of the seed region (physiological term). As for other aforementioned fMRI analyses, we performed t-test to compare the differences between the conditions.

3.1.4 Results

Behavioral results

The difficulty of the task was assessed by determining the number of trials which the participants answered correctly (i.e. the numerosity estimation of generated/heard words). On average, 19.9 % of all trials during the numerosity estimations were reported correctly; 16.89 % correct trials during the active condition and 21.88 % during the passive condition. We performed a Pearson's Chi-squared test of correctly and incorrectly estimated trials during the active/passive conditions (Chi2 = 3.72 p = 0.054).

Next, we computed the numerosity performance and found that in both conditions participants underestimated (M = -0.05, SD = 0.11, CI(95%) = [-0.06, -0.05]) the number of words. Interestingly, this underestimation was larger (F(1,24) = 5.85, p = 0.023, 18 subjects out of 25 showed the effect) in the active condition (M = -0.07, SD = 0.11, CI(95%) = [-0.08, -0.06]) compared to the passive condition (M = -0.04, SD = 0.12, CI(95%) = [-0.05, -0.03]) (Figure 2A). Comparable results were obtained during the pilot experiment in the mock scanner in an independent group of subjects. Again, participants underestimated the number of words more during the active condition (M = -0.05, SD = 0.01, CI(95%) = [-0.06, -0.03]) compared to the passive (M = -0.03, SD = 0.10, CI(95%) = [-0.04, -0.02]; F(1,16) = 5.80 p = 0.016).

We then assessed the linear relationship between the reported number of words (numerosity estimation) and the actual number of words. We found a main effect of words generated/heard (F(1,908) = 1042, p < 0.001) and condition (F(1,198) = 8.25, p = 0.0045) on numerosity estimations indicating, respectively, that the numerosity estimations differed for the different generated/heard words and also across both conditions. We also found an interaction between condition and generated/heard words (F(1,802) = 4.3, p = 0.038) with a steeper slope in the active condition (M = 0.62, CI(95%) = [0.57, 0.67]) compared to the passive condition (M = 0.55, CI(95%) = [0.50, 0.60]) (Figure 2B). These findings indicate better numerosity tracking for self-generated words during the main fMRI experiment (a slope of value 1 reflecting ideal performance) (Figure 2B). We note that nor the main effect of condition (F(1,143) = -0.04, p = 0.66), nor the interaction (F(1,350) = 1.10, p = 0.66) reached significance in our pilot experiment.

Finally, we investigated whether performance monitoring varied between conditions. This measure reflects how well participants were able to track the error made during the numerosity estimation. We found no differences in performance monitoring ($F(1,24) = 1.09$, $p = 0.3$) between the active ($M = 0.07$, $SD = 0.06$, $CI(95\%) = [0.07, 0.08]$) and passive ($M = 0.08$, $SD = 0.06$, $CI(95\%) = [0.07, 0.09]$) conditions during the fMRI experiment. Similar results were found during the mock scanner pilot experiment ($F(1,16) = 0.78$, $p = 0.39$; active: $M = 0.07$, $SD = 0.06$, $CI(95\%) = [0.06, 0.08]$; passive: $M = 0.06$, $SD = 0.06$, $CI(95\%) = [0.06, 0.07]$), confirming the absence of evidence supporting an effect of cognitive self-attenuation on performance monitoring.

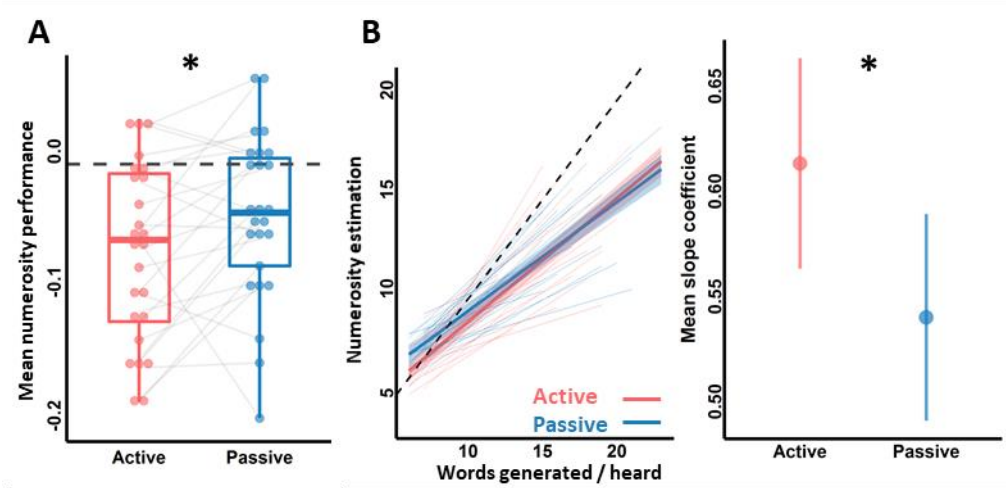

Figure 2. Behavioral results of the main fMRI experiment. (A) Individual numerosity performance in the active (red) and passive (blue) condition. A value of zero represents an ideal performance. Each dot represents a participant. Grey lines connect performance from the same participant across conditions (B) Left panel: Linear regression between numerosity estimation (reported number of words) and an actual number of words. Reference dashed line with a slope equal to 1 represents ideal performance. Thick lines represent the mean model fit of linear regression per condition, while thin lines depict the individual model fit. Right panel: mean slope coefficient estimates with 2.5% and 97.5% confidence intervals of linear regression that is higher during the active condition as compared to the passive condition.

Lastly, we carried out a control task for word generation outside the scanner, during which participants had to perform a standard verbal fluency task overtly with the cue letter ‘p’. Comparing the number of words generated, starting with the letter ‘p’ overtly (outside the scanner) and covertly (during the scanning), we did not observe any significant differences (paired t-test; $t(1,24) = -0.4$; $p=0.69$) between the number of words generated overtly ($M = 12.6$, $SD = 3.79$, $CI(95\%) = [10.9, 14.1]$) and covertly ($M = 12.3$, $SD = 3.96$, $CI(95\%) = [10.6,$

13.9]). This control task suggest that subjects did generate words covertly and comparably to overt fluency, according to the required rules.

fMRI results

Numerosity performance

Right IPS was activated during numerosity estimation and parametrically modulated by numerosity performance, independently from condition (main effect F = 20.0, pFWE = 0.042; Figure 3; Table 1). Activations in IPS were bilateral when using a less stringent threshold (p<0.005 peak level uncorrected; Table S1, Figure S2). However, IPS activation did not differ between the active and passive conditions, suggesting that this parietal activation was associated with the numerosity performance, independent of whether words were heard or actively generated. No other brain regions were associated with the numerosity performance.

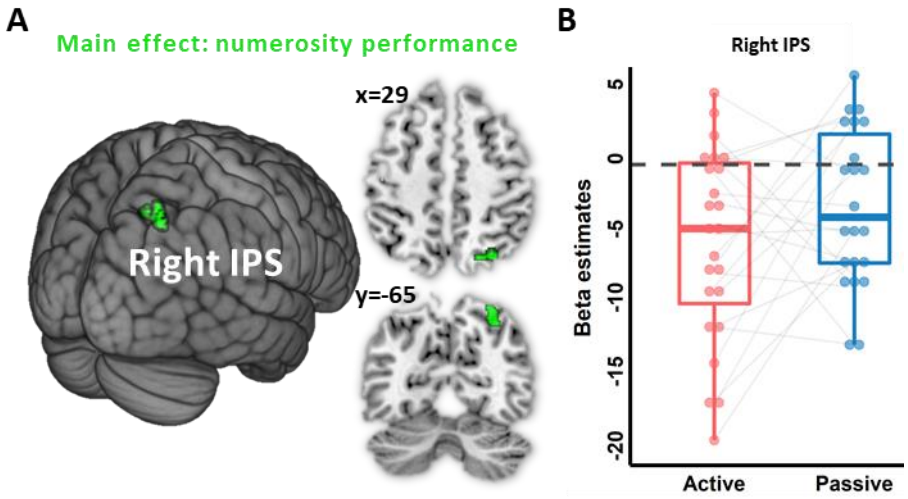

Figure 3. Neural correlates associated with numerosity performance. (A) Main effect (active+passive conditions) of the parametrically modulated numerosity performance during numerosity estimation in the left intraparietal sulcus (depicted in green). (B) Box plot of beta estimates in the right IPS during numerosity estimations parametrically modulated with numerosity performance. Grey lines connect beta estimates from the same participant across conditions.

				Peak voxel MNI coordinate				
BA	Anatomical Label		k	x	y	z	p_{FWE}	F
	Main effect (active + passive)							
7	Intraparietal sulcus (superior parietal g., angular g.)	R	148	29	-65	50	0.042	20

Table 1. The numerosity estimation is parametrically modulated with the numerosity performance. The list of brain areas is described where BOLD signal correlates with the trial-by-trial behavioral measures of

the numerosity performance during numerosity estimation. The data is voxel level p<0.001 uncorrected, cluster threshold at p<0.05 FWE corrected. BA – Broadmann area, k – cluster size, R – right hemisphere

With the PPI analysis, we investigated whether the functional coupling of the right IPS with other brain regions was modulated by the condition (active or passive). The bilateral supplementary motor area (SMA), left inferior parietal lobule (IPL) and left superior temporal gyrus (STG) showed different connectivity across conditions. We found increased connectivity of all three regions with the right IPS in the active compared to the passive condition (Figure 4, Table 2).

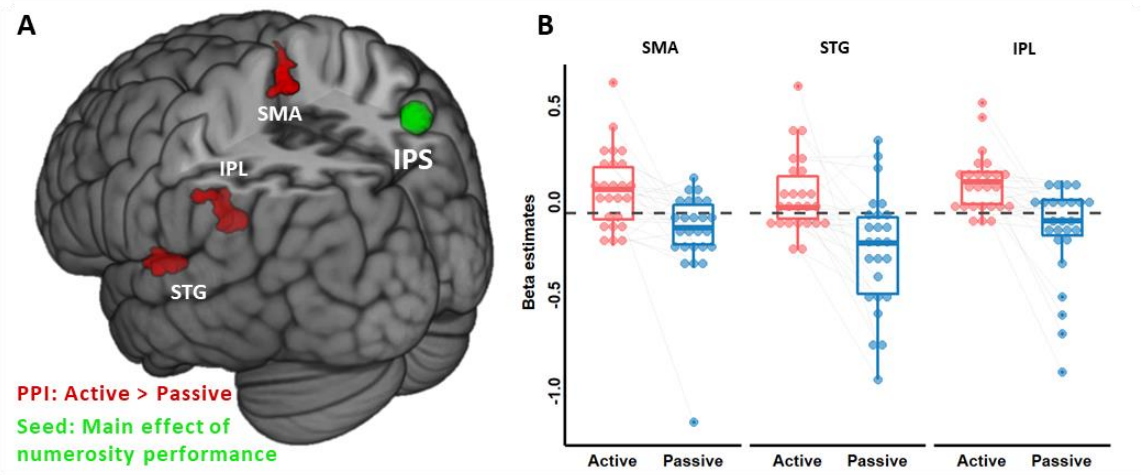

Figure 4. PPI analysis: numerosity estimation. (A) Stronger functional connectivity during the active condition as compared to the passive between the right intraparietal sulcus seed (depicted in green) and bilateral supplementary motor area (SMA), left inferior parietal lobule (IPL) and superior temporal gyri (STG), depicted in red. (C) Beta estimates of active and passive conditions are depicted in box plots for each significant cluster observed in PPI analysis. Grey lines connect beta estimates from the same participant across conditions.

BA	Anatomical Label		k	Peak voxel MNI coordinate x	y	z	p_{FWE}	T
	Active > passive							
41 42	Superior temporal g.	L	177	-54	-20	6	0.038	5.14
40	Supramarginal g., parietal inferior g.	L	291	-44	-42	29	0.003	5.14
6	Paracentral lobule, SMA	L/R	167	-3	-30	63	0.049	4.59

Table 2. PPI analysis: numerosity estimation. The list of BOLD activations of PPI analysis seeding from the right IPS during the numerosity estimation. The data is voxel level p<0.001 uncorrected, cluster threshold at p<0.05 FWE corrected. BA – Broadmann area, k – cluster size, R – right hemisphere, L – left hemisphere

We also searched for activation differences during numerosity estimations between conditions, independent of parametric modulations. We found widespread decreased activations in the active condition as compared to the passive condition. Major differential activations were found in bilateral middle-superior temporal gyri, precuneus, cerebellum, middle cingulate gyri, SMA, insula, middle-superior frontal gyri, hippocampus, caudate nucleus, putamen (for the detailed list of all areas see Table S2).

Performance monitoring

When looking at the parametric effects of performance monitoring, we observed that the BOLD signal in the left IPS was more related to performance monitoring in the active compared to the passive condition (T = 4.02, p_{FWE} = 0.041; Figure 5; Table 3). This activation cluster overlapped with the left intraparietal sulcus that was observed in the main effect of numerosity performance (see Figure S2).

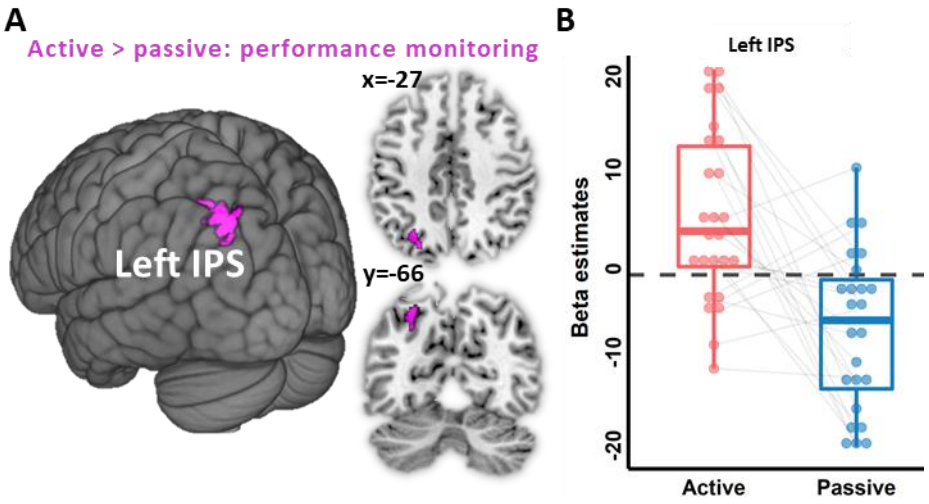

Figure 5. Neural correlates associated with performance monitoring. (A) Positive association between the trial-wise performance monitoring and BOLD signal during the error estimation active condition as compared to the passive in the left intraparietal sulcus (IPS, depicted in purple). (B) Box plot of beta estimates in the left IPS during error estimations parametrically modulated with error monitoring. Grey lines connect beta estimates from the same participant across conditions.

			Peak voxel MNI coordinate					
BA	Anatomical Label		k	x	y	z	p_{FWE}	T
	Active > passive							
7	Intraparietal sulcus (superior/inferior parietal g.)	L	198	-27	-66	47	0.041	4.02

Table 3. Error estimation parametrically modulated with performance monitoring. The list of brain areas where BOLD signal correlates with the trial-by-trial behavioral measures of the performance monitoring during the error estimation. The data is voxel level p<0.001 uncorrected, cluster threshold at p<0.05 FWE corrected. BA – Broadmann area, k – cluster size, L – left hemisphere

Results from the PPI analysis using the left IPS as a seed ROI, did not reveal any functional connectivity differences between the active and passive conditions during error estimation.

Lastly, analyzing activation differences between the active and passive conditions during the error estimation, we found increased overall activation (during both conditions) in the bilateral anterior insula and bilateral inferior frontal gyri, as well as the right putamen. Moreover, activations in these regions were significantly lower during the active condition compared to the passive condition (Figure 6; Table 4). In addition, increased activation during the active condition as compared to the passive was observed in the left caudate nucleus.

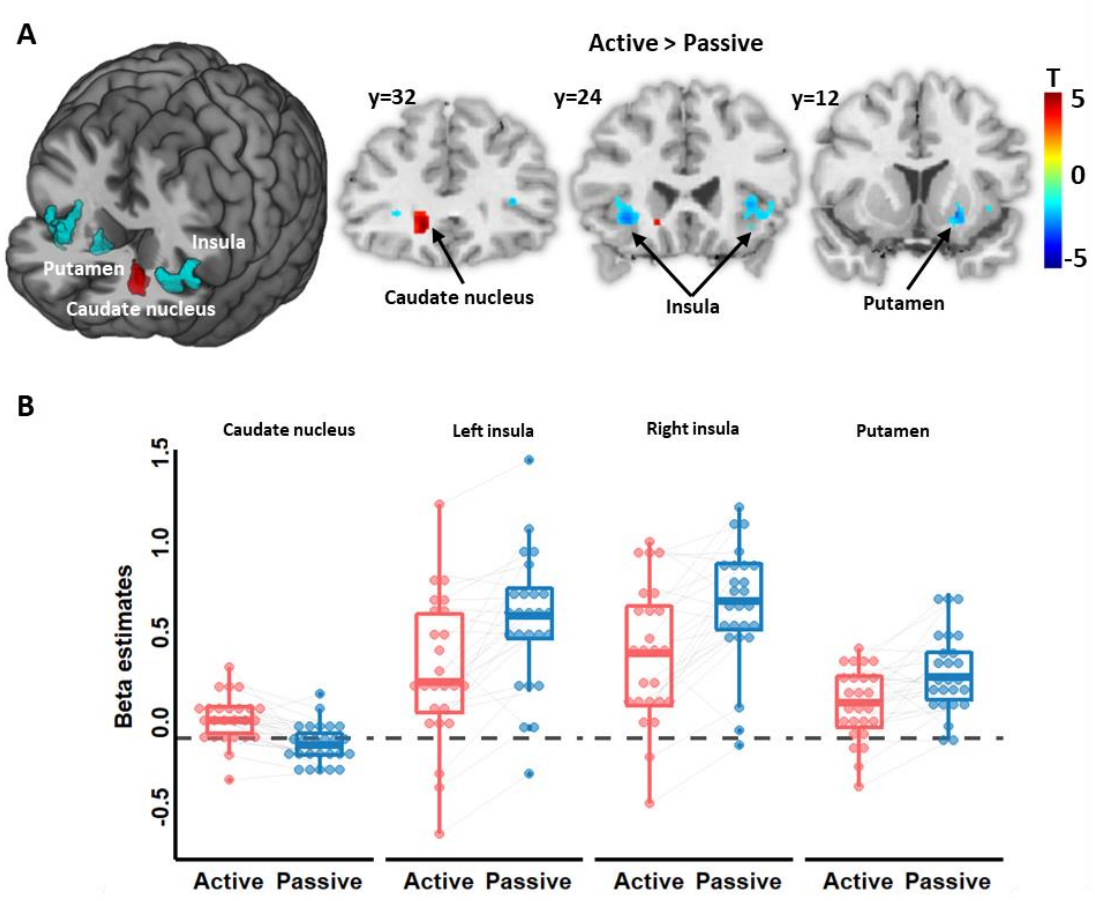

Figure 6. Activation differences during error estimation. (A) Decreased neural activity during the active condition as compared to the passive in the right putamen and insula bilaterally (depicted in blue). Increased activity during the active condition as compared to the passive was observed in the left caudate nucleus

(depicted in red). (B) Beta estimates of active and passive conditions are depicted in box plots for each significant cluster observed. Grey lines connect beta estimates from the same participant across conditions.

BA	Anatomical Label		k	Peak voxel MNI coordinate x	y	z	p_{FWE}	T
	Active > passive							
	Caudate nucleus	L	336	-15	30	-6	0.004	5.76
	Active < passive							
45 47 13	Insula, inferior frontal g. triangular part	L	392	-33	24	-6	0.002	5.3
	Putamen	R	209	20	12	-6	0.043	5.2
13 47 45	Insula, inferior frontal g. triangular part	R	482	32	27	0	0.000	4.3

Table 4. Error estimations. The list of BOLD signal activations during the error estimation, independent of parametric modulation. The data is voxel level p<0.001 uncorrected, cluster threshold at p<0.05 FWE corrected. BA – Broadmann area, k – cluster size, R – right hemisphere, L – left hemisphere

3.1.5 Discussion

The present study examined whether self-attenuation impacts cognitive processes beyond sensory systems, namely numerosity estimations and performance monitoring. To this end, we developed an experimental paradigm allowing a controlled comparison of numerosity estimations and performance monitoring regarding self and externally generated words while acquiring fMRI data. We found that participants underestimated more the number of self- compared to externally-generated words, providing behavioral evidence that numerosity estimations are indeed subject to self-attenuation. As expected, numerosity was associated with hemodynamic activity in the right IPS. Furthermore, a network including the bilateral SMA, left IPL and STG showed increased functional connectivity with the right IPS during numerosity estimations for self-generated words, suggesting an attenuation mechanism at the neural level. Finally, by asking participants to monitor the accuracy of their own numerosity estimations, we found equivalent performance monitoring for self- and externally-generated words, although neurally it was more associated with the left IPS during the active condition. In sum, these results provide behavioral and neural evidence that self-attenuation extends to cognitive processes beyond sensory system but does not impact the precision of performance monitoring.

Behavioral and neural markers of attenuated numerosity estimations

Participants underestimated the number of words they generated or heard. Such underestimation was previously described regarding the numeric estimation of perceptual quantities (e.g., number of dots or sequences of sounds) to a discrete measure (e.g., Arabic numeral) (45–48). In our study, we found, that word numerosity underestimation was stronger in the active compared to the passive condition, in line with our hypothesis that self-attenuation impacts cognitive processes (12,14,15). Of note, the number of accurate numerosity estimation trials where participants correctly reported the number of generated or heard words did not differ between conditions, ruling out that the underestimation of self-generated words (active condition) was due to potential experimental confounds between conditions.

Self-attenuation has been previously observed for sensory processes and refers to the diminished behavioral and neural responses associated with self-generated compared to

externally-generated stimuli (3,6,7). Importantly, self-attenuation is also known to be triggered by imagined actions in the absence of overt actions (e.g, 12,14,15). For example, the imagined self-touch was felt as less intense compared to the external touch (12), or imagined speech elicit reduced electrophysiological signal in the domain specific sensory cortex (14). These studies have investigated cognitive processes related to sensorimotor systems, yet, to our knowledge, it was unknown whether self-attenuation also affects higher-level cognition beyond sensorimotor processing. Here we showed that self-attenuation can be observed for cognitive processes such as numerosity estimations that do not involve sensorimotor processing. One leading theory of sensory self-attenuation is the internal forward model (49,50). It assumes that an efference copy of motor actions is used to predict the sensory consequences of that action (forward model). When such sensory predictions match the actual sensory feedback from the action, the latter is perceived as self-generated and its sensory consequences are attenuated (51). The forward model account thus links sensory attenuation to the absence of a prediction error generated by a neural comparator. A similar mechanism has been proposed to explain self-attenuation after covert actions such as motor imagery (12) or inner speech (52). As argued in the introduction, our study differs in that no sensory output is available as an input for the comparator to generate a prediction error. Therefore, one possibility is that numerosity underestimation stems from a weaker perceptual representation of self-generated words, similar to what is described for inner speech. In other word, self-attenuation would not impact numerosity directly, but through a decreased perceptual strength of estimated words. In this framework, both the number of self-generated words and passively-generated words played at low intensity should be similarly underestimated. Another, arguably more parsimonious explanation would be that covert mental operations have a gating effect (53), independent from predictive mechanisms, thereby directly affecting the strength of the mental representations of self-generated words. Such a mechanism could be advantageous in prioritizing the processing of external events. A similar gating mechanism has recently been shown to offer a plausible alternative to forward model accounts of sensory self-attenuation (54).

At the neural level, the IPS showed activity related to numerosity performance in line with previous studies (55–57). This relation, however, was not modulated by condition (active vs. passive), which could have been expected if self-attenuation directly impacted numerosity and not the perceptual strength of self-generated words (6,9). We nonetheless found an

increase in functional coupling during numerosity estimations in the active condition. This increase in coupling occurred between the IPS and a network comprising the SMA, IPL and STG, happen to be involved in auditory language and imagery (27–29), which further supports that numerosity underestimation stems from a weaker perceptual representation of self-generated words. Of note, we also found widespread decreases in hemodynamic activity during numerosity estimations in the active condition vs. the passive condition.

Besides this global self-attenuation effect, we found that participants formed more accurate numerosity estimations for self vs. externally-generated words: while participants' word estimations were lower in the active condition than in the passive condition, the relation between their estimated number of words and the actual number of words was better in the active condition compared to the passive condition, suggesting a sharper representation of the number of self-generated words. This result corroborates our recent findings (58), showing better monitoring for decisions that are committed rather than observed. This improved monitoring of self-generated words could be related to the sharpening of expected representations known in the sensory domain (59), or to a self-generation effect underlying the facilitation of information encoding and enhanced recall for self-generated stimuli (60,61).

Performance monitoring is modulated at the neural but not behavioral level

Previous research has shown that both humans and non-human primates (62–64) can monitor their numerosity estimations. Thus, in addition to asking participants to estimate the number of words they generated or heard, we also asked them to estimate their own error during the numerosity estimations. Although our behavioral results showed similar performance monitoring between conditions, we observed several regions that differentiated such performance monitoring between the active and passive conditions. At the neural level, we found that better performance monitoring was associated with hemodynamic activity in the left IPS. Interestingly, this region is not typically associated with performance monitoring such as the posterior medial frontal cortex, the insula/inferior frontal gyrus or the prefrontal cortex (65). Since activity in the left IPS is related to numerosity estimation (66,67), this parametric modulation could therefore represent a substrate for monitoring specific to numerosity estimations. Similar domain-specific regions have been found for perceptual versus memory introspection (68). Yet, when investigating global hemodynamic activity during the error estimation about the performed numerosity judgement, we observed decreased activation in

the insula and putamen and increased activity in the caudate nucleus in the active compared to the passive conditions. To note, anterior insula and putamen were activated during both conditions but with attenuated activation during the active compared to the passive conditions. While the anterior insula activations were expected from the previous literature about the performance monitoring (69–71), the findings of modulated activity between the conditions in the putamen and the caudate nucleus were unexpected. These areas are known as essential regions for control of goal-directed decision-making (72,73) suggesting that different activation of these regions between conditions could have acted as an alternative cognitive mechanism impacting similar performance monitoring.

Conclusion

Based on behavioral and neuroimaging data, we propose that higher-level cognitive functions such as numerosity estimations about the number of self-generated words are attenuated. Such attenuation involves a functional network including a key-numerosity region (IPS) and speech-related regions including the SMA, IPL and STG. While attenuating the sensory consequences of one's actions is of crucial importance for aspects of the self, such as the sense of agency, attenuating the by-products of one's mental activities may be relevant to distinguish them from external sources of information. Our paradigm offers a promising tool to investigate attenuation processes related to the self in cognition, and to distinguish them from sensory attenuation processes. It may be of relevance to study clinical cases in which attenuation in sensory and cognitive domains is altered, including patients with psychotic symptoms like thought insertion whereby thoughts are not considered as one's own, but of somebody else.

3.1.6 References

1. Kircher T, David A. The Self in Neuroscience and Psychiatry. Kircher T, David A, editors. The self in neuroscience and psychiatry. Cambridge: Cambridge University Press; 2003. 147–165 p.
2. Legrand D. The bodily self: The sensori-motor roots of pre-reflective self-consciousness. Phenomenol Cogn Sci. 2006;5(1):89–118.
3. Timm J, SanMiguel I, Keil J, Schröger E, Schönwiesner M. Motor Intention Determines Sensory Attenuation of Brain Responses to Self-initiated Sounds. J Cogn Neurosci. 2014 Jul;26(7):1481–9.
4. Baess P, Horváth J, Jacobsen T, Schröger E. Selective suppression of self-initiated sounds in an auditory stream: An ERP study. Psychophysiology. 2011;48(9):1276–83.
5. Hughes G, Waszak F. ERP correlates of action effect prediction and visual sensory attenuation in voluntary action. Neuroimage. 2011;56(3):1632–40.
6. Benazet M, Thénault F, Whittingstall K, Bernier PM. Attenuation of visual reafferent signals in the parietal cortex during voluntary movement. J Neurophysiol. 2016;116(4):1831–9.
7. Shergill SS, White TP, Joyce DW, Bays PM, Wolpert DM, Frith CD. Modulation of somatosensory processing by action. Neuroimage. 2013;70:356–62.
8. Kilteni K, Ehrsson HH. Functional connectivity between the cerebellum and somatosensory areas implements the attenuation of self-generated touch. J Neurosci. 2019 Dec 6;1732–19.
9. Whitford TJ. Speaking-Induced Suppression of the Auditory Cortex in Humans and Its Relevance to Schizophrenia. Biol Psychiatry Cogn Neurosci Neuroimaging. 2019;4(9):791–804.
10. Brooks JX, Cullen KE. Predictive Sensing: The Role of Motor Signals in Sensory Processing. Biol Psychiatry Cogn Neurosci Neuroimaging. 2019;4(9):842–50.
11. Bansal S, Ford JM, Spering M. The function and failure of sensory predictions. Ann N Y Acad Sci. 2018;1426(1):199–220.
12. Kilteni K, Andersson BJ, Houborg C, Ehrsson HH. Motor imagery involves predicting the sensory consequences of the imagined movement. Nat Commun. 2018;9(1):1–9.
13. Scott M, Yeung HH, Gick B, Werker JF. Inner speech captures the perception of external speech. J Acoust Soc Am. 2013;133(4):EL286–92.
14. Whitford TJ, Jack BN, Pearson D, Griffiths O, Luque D, Harris AWF, et al. Neurophysiological evidence of efference copies to inner speech. Elife. 2017;6:1–23.
15. Jack BN, Le Pelley ME, Han N, Harris AWF, Spencer KM, Whitford TJ. Inner speech is accompanied by a temporally-precise and content-specific corollary discharge. Neuroimage 2019;198(March):170–80.
16. Ylinen S, Nora A, Leminen A, Hakala T, Huotilainen M, Shtyrov Y, et al. Two distinct auditory-motor circuits for monitoring speech production as revealed by content-specific suppression of auditory cortex. Cereb Cortex. 2015;25(6):1576–86.
17. Scott M. Corollary Discharge Provides the Sensory Content of Inner Speech. Psychol Sci. 2013;24(9):1824–30.
18. Poeppel D. The neuroanatomic and neurophysiological infrastructure for speech and language. Curr Opin Neurobiol. 2014;28:142–9.

19. Hickok G, Poeppel D. The cortical organization of speech processing. Nat Rev Neurosci. 2007 May 13;8(5):393–402. Available from: http://www.nature.com/articles/nrn2113
20. Liebenthal E, Binder JR, Spitzer SM, Possing ET, Medler DA. Neural substrates of phonemic perception. Cereb Cortex. 2005;15(10):1621–31.
21. DeWitt I, Rauschecker JP. Phoneme and word recognition in the auditory ventral stream. Proc Natl Acad Sci U S A. 2012;109(8):505–14.
22. Rummell BP, Klee JL, Sigurdsson T. Attenuation of responses to self-generated sounds in auditory cortical neurons. J Neurosci. 2016;36(47):12010–26.
23. Dehaene S. The Number Sense. Oxford Univ. Press; 1997.
24. Burr DC, Anobile G, Arrighi R. Psychophysical evidence for the number sense. Philos Trans R Soc B Biol Sci. 2018;373(1740).
25. Anobile G, Cicchini GM, Burr DC. Number As a Primary Perceptual Attribute: A Review. Perception. 2016;45(1–2):5–31.
26. Arsalidou M, Taylor MJ. Is 2+2=4? Meta-analyses of brain areas needed for numbers and calculations. Neuroimage. 2011;54(3):2382–93.
27. Rauschecker JP, Scott SK. Maps and streams in the auditory cortex: Nonhuman primates illuminate human speech processing. Nat Neurosci. 2009;12(6):718–24.
28. Tian X, Zarate JM, Poeppel D. Mental imagery of speech implicates two mechanisms of perceptual reactivation. Cortex. 2016;77:1–12.
29. Lima CF, Krishnan S, Scott SK. Roles of Supplementary Motor Areas in Auditory Processing and Auditory Imagery. Trends Neurosci. 2016;39(8):527–42.
30. Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia. 1971;9(1):97–113.
31. Kleiner M, Brainard DH, Pelli DG, Broussard C, Wolf T, Niehorster D. What's new in Psychtoolbox-3? Perception. 2007;36:S14.
32. Brainard DH. The Psychophysics Toolbox. Spat Vis. 1997;10(4):433–6.
33. Pelli DG. The VideoToolbox software for visual psychophysics: Transforming numbers into movies. Spat Vis. 1997;10(4):437–42.
34. Ferrand L, Alario F-X. Normes d'associations verbales pour 366 noms d'objets concrets. Annee Psychol. 1998;98(4):659–709.
35. Lezak MD. Neuropsychological assessment (3rd ed.). Neuropsychological assessment (3rd ed.). 1995. 544–546 p.
36. Fleming SM, Lau HC. How to measure metacognition. Front Hum Neurosci. 2014;8(July):1–9.
37. Cowan N. The magical mystery four: How is working memory capacity limited, and why? Curr Dir Psychol Sci. 2010;19(1):51–7.
38. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4 | Bates | Journal of Statistical Software. J Stat Softw. 2015;67(1).
39. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest Package: Tests in Linear Mixed Effects Models . J Stat Softw. 2017;82(13).
40. Luke SG. Evaluating significance in linear mixed-effects models in R. Behav Res Methods. 2017;49(4):1494–502.

41. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage. 2012;59(3):2142–54.
42. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage. 2002;15(1):273–89.
43. Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. Neuroimage. 1997;6(3):218–29.
44. McLaren DG, Ries ML, Xu G, Johnson SC. A generalized form of context-dependent psychophysiological interactions (gPPI): A comparison to standard approaches. Neuroimage. 2012 Jul;61(4):1277–86.
45. Reinert RM, Hartmann M, Huber S, Moeller K. Unbounded number line estimation as a measure of numerical estimation. PLoS One. 2019;14(3):1–16.
46. Pecunioso A, Miletto Petrazzini ME, Agrillo C. Anisotropy of perceived numerosity: Evidence for a horizontal–vertical numerosity illusion. Acta Psychol (Amst). 2020;205(January):103053.
47. Castronovo J, Seron X. Numerical Estimation in Blind Subjects: Evidence of the Impact of Blindness and Its Following Experience. J Exp Psychol Hum Percept Perform. 2007;33(5):1089–106.
48. Crollen V, Castronovo J, Seron X. Under- and over-estimation: A bi-directional mapping process between symbolic and non-symbolic representations of number? Exp Psychol. 2011;58(1):39–49.
49. Miall RC, Wolpert DM. Forward models for physiological motor control. Vol. 9, Neural Networks. 1996. p. 1265–79.
50. Farrer C, Frith CD. Experiencing oneself vs another person as being the cause of an action: The neural correlates of the experience of agency. Neuroimage. 2002;15(3):596–603.
51. Wolpert DM, Flanagan JR. Motor prediction. Curr Biol. 2001;11(18):729–32.
52. Tian X, Poeppel D. Mental imagery of speech and movement implicates the dynamics of internal forward models. Front Psychol. 2010;1(OCT):1–23.
53. Cromwell HC, Mears RP, Wan L, Boutros NN. Sensory gating: A translational effort from basic to clinical science. Clin EEG Neurosci. 2008;39(2):69–72.
54. Thomas ER, Yon D, Lange FP de, Press C. Action enhances predicted touch. bioRxiv. 2020;2020.03.26.007559.
55. Dehaene S, Cohen L. Two mental calculation systems: A case study of severe acalculia with preserved approximation. Neuropsychologia. 1991;29(11):1045–74.
56. Cohen L, Dehaene S. Cerebral Networks for Number Processing: Evdence from a Case of Posterior Callosal Lesion. Neurocase. 1996;2(3):155–74.
57. Piazza M, Mechelli A, Price CJ, Butterworth B. Exact and approximate judgements of visual and auditory numerosity: An fMRI study. Brain Res. 2006;1106(1):177–88.
58. Pereira M, Faivre N, Iturrate I, Wirthlin M, Serafini L, Martin S, et al. Disentangling the origins of confidence in speeded perceptual judgments through multimodal imaging. Proc Natl Acad Sci. 2020 Apr 14;117(15):8382–90.
59. Kok P, Jehee JFM, de Lange FP. Less Is More: Expectation Sharpens Representations in the Primary Visual Cortex. Neuron. 2012;75(2):265–70.

60. Slamecka NJ, Graf P. The generation effect: Delineation of a phenomenon. J Exp Psychol Hum Learn Mem. 1978;4(6):592–604.
61. Bertsch S, Pesta BJ, Wiscott R, McDaniel MA. The generation effect: A meta-analytic review. Mem Cogn. 2007;35(2):201–10.
62. Beran MJ, Smith JD, Redford JS, Washburn DA. Rhesus macaques (Macaca mulatto) monitor uncertainty during numerosity judgments. J Exp Psychol Anim Behav Process. 2006;32(2):111–9.
63. Duyan YA, Balcı F. Numerical error monitoring. Vol. 25, Psychonomic Bulletin and Review. 2018. p. 1549–55.
64. Duyan YA, Balcı F. Metric error monitoring in the numerical estimates. Vol. 67, Consciousness and Cognition. 2019. p. 69–76.
65. Vaccaro AG, Fleming SM. Thinking about thinking: A coordinate-based meta-analysis of neuroimaging studies of metacognitive judgements. Brain Neurosci Adv. 2018;2:239821281881059.
66. Cappelletti M, Barth H, Fregni F, Spelke ES, Pascual-Leone A. rTMS over the intraparietal sulcus disrupts numerosity processing. Exp Brain Res. 2007 Jun 11;179(4):631–42. Available from: http://link.springer.com/10.1007/s00221-006-0820-0
67. Dormal V, Andres M, Pesenti M. Contribution of the right intraparietal sulcus to numerosity and length processing: An fMRI-guided TMS study. Cortex. 2012;48(5):623–9.
68. Morales J, Lau H, Fleming SM. Domain-General and Domain-Specific Patterns of Activity Supporting Metacognition in Human Prefrontal Cortex. J Neurosci. 2018;38(14):3534–46.
69. Ullsperger M, Harsay HA, Wessel JR, Ridderinkhof KR. Conscious perception of errors and its relation to the anterior insula. Brain Struct Funct. 2010;214(5–6):629–43.
70. Bastin J, Deman P, David O, Gueguen M, Benis D, Minotti L, et al. Direct Recordings from Human Anterior Insula Reveal its Leading Role within the Error-Monitoring Network. Cereb Cortex. 2017;27(2):1545–57.
71. Klein TA, Ullsperger M, Danielmeier C. Error awareness and the insula: Links to neurological and psychiatric diseases. Front Hum Neurosci. 2013;7(JAN):1–14.
72. Balleine BW, Delgado MR, Hikosaka O. The role of the dorsal striatum in reward and decision-making. J Neurosci. 2007;27(31):8161–5.
73. Kim BS, Im HI. The role of the dorsal striatum in choice impulsivity. Ann N Y Acad Sci. 2019;1451(1):92–111.

3.1.7 Supplementary Information

Data simulation of derived measures of numerosity performance and performance monitoring

We simulated data to see how derived measurements of numerosity performance and performance monitoring behave in every possible situation before applying it to the real data. The measurements should be applicable not only to our data set but as well to any other ordinal data. However, for the simulations we have restricted the range within the limits of expected subject behavior. The actual number of words and numerosity estimation (reported number of words) ranged between 5 and 20. Error estimation varied between 0 and 5. Data simulation of numerosity performance confirms that underestimation and overestimation are linearly changing with the same weight (Figure S1 A). The performance monitoring considers the difficulty of the task. In other words, if the number of words increases, the performance monitoring value will not be as high as for a small stimulus even though the subject chose the same value for the error estimation (Figure S1 B, C).

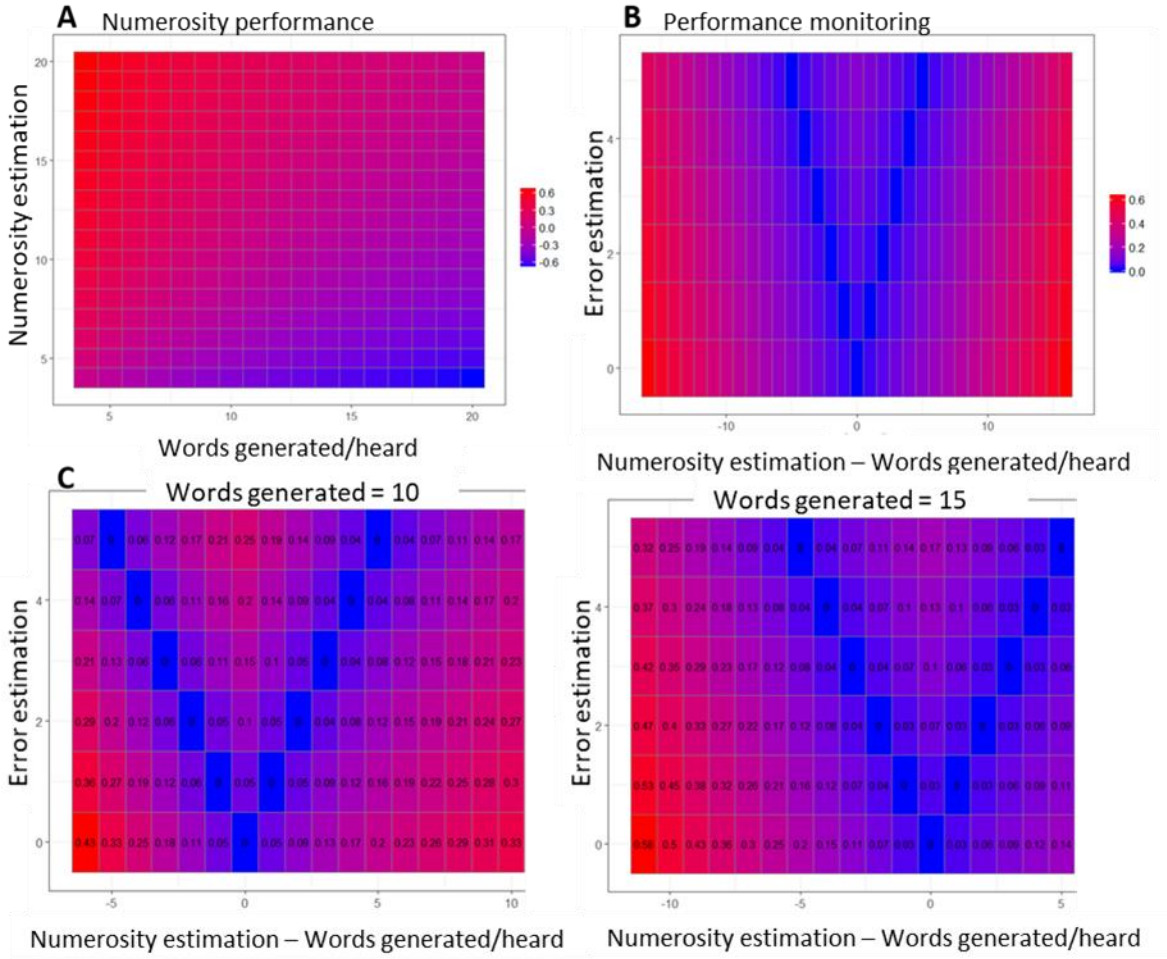

Figure S1. Data simulation of behavioral performance measures. (A) Simulated numerosity performance. (B) Simulated performance monitoring. (C) Simulated performance monitoring with represented values when the number of words is constant (10 or 15 words).

BA	Anatomical Label		k	Peak voxel MNI coordinate x	y	z	p_{FWE}	T
	Active < passive							
	Middle temporal g. Precuneus Superior temporal g. Postcentral Middle cingulum Cerebellum SMA Insula Precentral Supramarginal g. Angular g. Superior parietal Putamen Middle frontal g. Caudate Superior fontal g. Superior parietal g. Calcarine Rolandic percular Supramarginal g. Thalamus Hippocampus Fusiform g. Inferior temporal g. Lingual g. Cuneus Occipital g.	L/R	113587	20	8	-12		9.75
	Thalamus	L	314	-11	-23	15		6.84
10	Middle frontal g.	L	442	-36	50	27		4.97
10	Middle frontal g.	R	399	29	53	32		4.69

Table S1. Numerosity estimation. The list of BOLD signal activations during the numerosity estimation, independent of parametric modulation. The data is voxel level p<0.001 uncorrected, cluster threshold at p<0.05 FWE corrected. BA – Broadmann area, k – cluster size, R – right hemisphere, L – left hemisphere, R right hemisphere

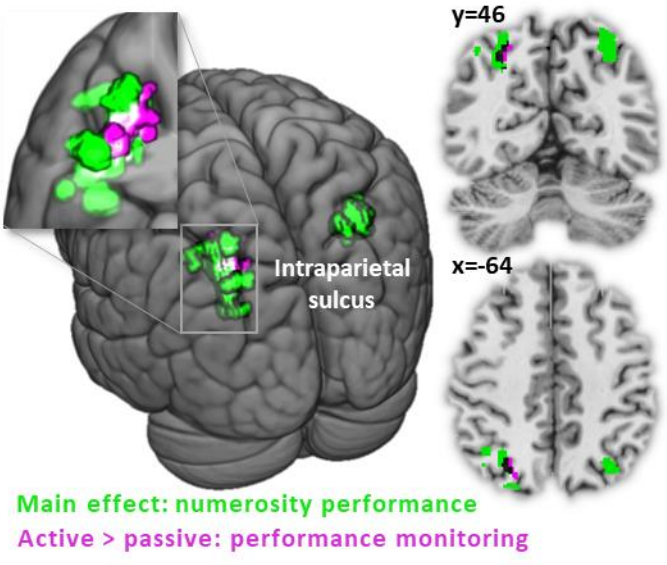

Figure S2. The overlap between the neural correlates associated with parametric modulators. A positive association between the trial-wise performance monitoring and BOLD signal during the error estimation active condition as compared to the passive in the left intraparietal sulcus (depicted in purple); peak level uncorrected p<0.001. Main effect (active+passive conditions) of numerosity performance during the numerosity estimation in the bilateral intraparietal sulcus (depicted in green); peak level uncorrected p<0.005. The left intraparietal sulcus partly overlaps (114 voxels) with the activation associated with the performance monitoring during the active compared to the passive condition.

				Peak voxel MNI coordinate				
BA	Anatomical Label		k	x	y	z	p_{FWE}	T
	Main effect (active + passive)							
7	Intraparietal sulcus (superior parietal g., angular g.)	R	466	29	-65	50	0.004	20
7	Intraparietal sulcus (superior/inferior parietal g., middle occipital g.)	L	758	-30	-63	42	0.000	15.9

Table S2. Numerosity estimation parametrically modulated with numerosity performance. The list of brain areas where BOLD signal correlates with the trial-by-trial behavioral measures of the numerosity performance during the numerosity estimation. The data is voxel level p<0.005 uncorrected, cluster threshold at p<0.05 FWE corrected. BA – Broadmann area, k – cluster size, R – right hemisphere, L – left hemisphere

3.2 STUDY 4: THE COGNITIVE AND SENSORIMOTOR BRAIN MECHANISMS OF THOUGHT INSERTION

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Author Contributions

GS, PPO, OB developed the study concept and contributed to the study design. Testing and data collection were performed by JP, PPR, PPO, KD, PC, and PH. GS performed the data analysis. GS, JP, and OB drafted the paper; all authors provided critical revisions and approved the final version of the article for submission.

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Disclosure statement

The authors report no conflict of interest.

3.2.1 Abstract

Thought Insertion (TI) is one of the most enigmatic psychotic passivity experiences described by certain thoughts arising in one's mind that are generated not by oneself but by somebody else. Here, we recruited first-episode psychotic patients with (N=21) and without TI (N=21) and healthy controls (N=18) to investigate the cognitive and sensorimotor brain mechanisms related to this phenomenon. Given that self-other distinction important to the subjective experience, such as the sense of agency, is associated with the attenuation of self-generated stimuli, we studied whether the self-attenuation is affected in psychotic patients with TI. To do so, we employed a novel paradigm where we have investigated self-attenuation during the higher-level cognitive function of numerosity estimations and how it is related to the affected executive functions. Next, we have studied neural mechanisms related to attenuation processing during numerosity estimations and, additionally, the ones (PH-network) related to the alienation aspect of TI (the experience of an alien entity inserting the thoughts). We showed that self-attenuation is occurring during the cognitive function of numerosity estimations in all participants. Importantly, we found a negative association between the affected executive functions and varying levels of cognitive self-attenuation only in psychotic patients with TI. This finding suggests that the TI is related to altered higher-level cognitive functioning. Further, we showed functional connectivity increase within the network involved in the attenuation processing during the numerosity estimations, suggesting insufficient attenuation at the neural level. Lastly, we report functional connectivity reduction within the PH-network between fronto-temporal and temporal areas in psychotic patients with TI, corroborating the disconnection hypothesis for hallucinations. Crucially, we reported a positive correlation between the cognitive-self attenuation and increased connectivity within the left frontal areas of the PH-network. Together, these findings revealed that different aspects related to cognitive and sensorimotor self-monitoring are affected in patients with TI, giving a better understanding of the mechanisms involved in this phenomenon.

3.2.2 Introduction

Self-generated sensory events attenuate perceptual and neural signals compared to sensory events from other agents or environmental sources (e.g., 1–3). Indeed, at the behavioral level attenuation of self-generated stimuli have been reported to supress the perception of auditory (e.g., 4) or somatosensory (e.g., 5) signals. At the neural level, such self-attenuation has also been revealed in primary sensory regions, such as self-generated auditory stimuli leading to attenuation in auditory cortex (6), and in areas outside sensory cortex such as thalamus, cerebellum, or inferior parietal lobule (7,8). Attenuation of self-generated stimuli has been argued to be important for source-monitoring, defined as an ability to distinguish self-generated perceptions, actions, or thoughts from externally generated ones (9–12) and is assumed to result from sensory prediction signals that are associated with our own actions (13).

Source-monitoring and sensory prediction for self-generated signals has also been proposed as an important mechanism in psychosis (14–16). Thus, it has been argued that psychotic symptoms such as passivity experiences (17,18), where self-generated perceptions, actions, or thoughts are not perceived as one's own and misattributed to an external agent are caused by impairments in self-monitoring (9,19–21). Notably, several studies have reported reduced sensory attenuation at the behavioral and neural level, when psychotic patients are exposed to self-generated sensory stimuli in the auditory (22,23) and somatosensory domains (24,25), arguing that the loss of self-attribution and otherness of passivity experiences (for example auditory verbal hallucinations or thought insertion) is directly related to alterations in self-monitoring characterized by reduced self-attenuation (6,8,22–25).

Nonetheless, whereas the importance of self-attenuation and related sensory signalling and their breakdown in psychotic symptoms is well established for symptoms associated with self-generated actions, it is not known whether and how this concept applies to other important psychotic symptoms such as auditory verbal hallucinations or common delusions like thought insertion (TI). TI is defined as the experience that certain thoughts, occurring in one's mind, are not one's own, but rather the thoughts of somebody else (26,27). TI violates basic intuitions about consciousness, is often reported by patients with schizophrenia and other psychotic disorders, and is classified as a passivity experience, implying that a regular

occurrence is suggestive of a psychotic disorder (28). There exist proposals that TI is related to non-sensory cognitive function alterations contributing to different context of thought generation (29–31). Thoughts can manifest in various forms such as memories, mind wandering, goal-directed while performing a task that involve covert language, mental operations or recalling images (32,33). However, it has been also suggested that TI is a form of auditory verbal hallucinations and thus auditory self-monitoring during inner speech is affected (34–37). Notably, TI is occurring in more than 30% of patients with schizophrenia (38,39), but despite its high occurrence, there is currently no accepted empirical model that explains TI (11,31), although recently methods have been developed to induce milder mental states comparable to symptomatic TI (e.g., 40–42). Thus, there is currently no accepted neuroscience account of TI and it is not known whether and how TI relates to alterations of source monitoring.

Recently, our group has extended research in sensory attenuation and related source-monitoring from sensorimotor processing to cognitive processing that may be important for understanding source monitoring in TI. Thus, Stripeikyte et al. (in preparation) showed that a cognitive task, numerosity estimations, defined as approximate judgments when counting is not involved (43) are a subject to self-attenuation when these are self-generated. Participants were either self-generating or passively hearing a list of words and the data showed that numerosity estimations of self-generated (active condition) versus externally-generated words (passive condition), was characterized by systematic underestimation (attenuation). This cognitive self-attenuation was further linked to a network consisting of right intraparietal sulcus (IPS), a key area associated with numerosity estimations (e.g., 44), as well as bilateral supplementary motor area (SMA), left inferior parietal lobule (IPL), and left superior temporal gyrus (STG).

In the present study, we aimed at understanding the mechanisms of TI by investigating the behavioural and neural mechanisms of numerosity estimations in psychotic patients with TI. We investigated whether self-attenuation during numerosity estimations can be observed at the behavioral and neural level and how this differed in three groups, psychotic patients with TI, psychotic patients without TI, and healthy controls, using the paradigm developed by Stripeikyte et al. (in preparation). We expected to replicate self-attenuation in the active as compared to the passive condition in all three groups (45) and, further, hypothesized that

numerosity self-attenuation would be more reduced (less underestimated) in psychosis patients with TI versus patients without TI as shown for sensory self-attenuation in sensory domains in schizophrenic patients (6,8). Concerning the neural mechanisms, we analysed the numerosity network (45) and expected to observe increased functional connectivity of the numerosity network in the patients with TI versus those without TI as observed for self-attenuation in sensory cortices in patients with schizophrenia (6,8). Additionally, we also investigated connectivity in a second network that has recently been shown to be involved in psychosis and specific hallucinations (e.g., presence hallucination network; PH-network; 18,46) and, importantly, experimentally-induced TI in healthy subjects (40).

3.2.3 Methods

Participants

Forty-two patients diagnosed with first-episode psychosis and eighteen healthy controls were included in this study. Patients, who met threshold criteria for psychosis, as defined by the 'Psychosis threshold' subscale of the Comprehensive Assessment of At-Risk Mental States, were recruited from the TIPP Program (Treatment and Early Intervention in Psychosis Program, University Hospital, Lausanne, Switzerland) (47). The study's exclusion criteria were history of neurological illness or trauma, non-psychiatric visual or auditory disorders, diagnosis of psychosis related intoxication or organic brain disease, intelligence quotient <70, age below 18 and above 35. The healthy control (CTRL) group was recruited via the TIPP program's control cohort and had no history of psychiatric disease or first-degree relatives with a history of psychotic disorder. Written informed consent (protocol approved by the Cantonal Ethics Commission of Vaud, Switzerland) was obtained for all participants.

Patients underwent an in-depth clinical assessment by a trained psychiatrist where the frequency and severity of symptoms were evaluated. The lifetime occurrence of thought insertion (TI) as described in item 18 of the Scale for the Assessment of Positive Symptoms (SAPS; 48) was assessed. Twenty-one patients had already presented TI during their psychotic episode and were assigned to the TI+ group. Twenty-one patients had never presented TI symptom and were thus included in the TI- group. Symptom severity was assessed in the patient groups using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The study was performed retrospectively, meaning that the imaging and neuropsychological data of participants were collected not at the same time as behavioral numerosity estimation experiment. The average time difference between the assessments was 1.5 years.

Numerosity estimation experiment

Task. The experiment contained a phonetic verbal fluency (50) and passive word-listening tasks, followed by numerosity estimations of their performance (Figure 1). The task consisted of two conditions during which participants either overtly generated words (active condition) or listened to pre-recorded words (passive condition). In the active condition, a starting phoneme (e.g., phoneme 'A') was played to participants through headphones and they were instructed to generate as many words starting with the cued phoneme as they could in a given

time period (e.g., apple, animal, alarm), which randomly varied between 15 s and 30 s. The experimenter counted and registered the words, and immediately afterward, the participant had to estimate how many words she or he had generated (without actually counting them). In the passive condition, the participants listened to a list of words, consisting of between 6 and 10 words. The number randomly varied throughout the trials. To prevent participants from counting the words and match the conditions for attention and cognitive load, they had to determine whether each word they heard contains a phoneme, specified at the beginning of a trial in the passive condition (e.g., man – yes, people – no). The words were played to participants with an inter-stimulus interval of 2.5 s. After the participants listened to the words, they immediately had to estimate the total number of words heard.

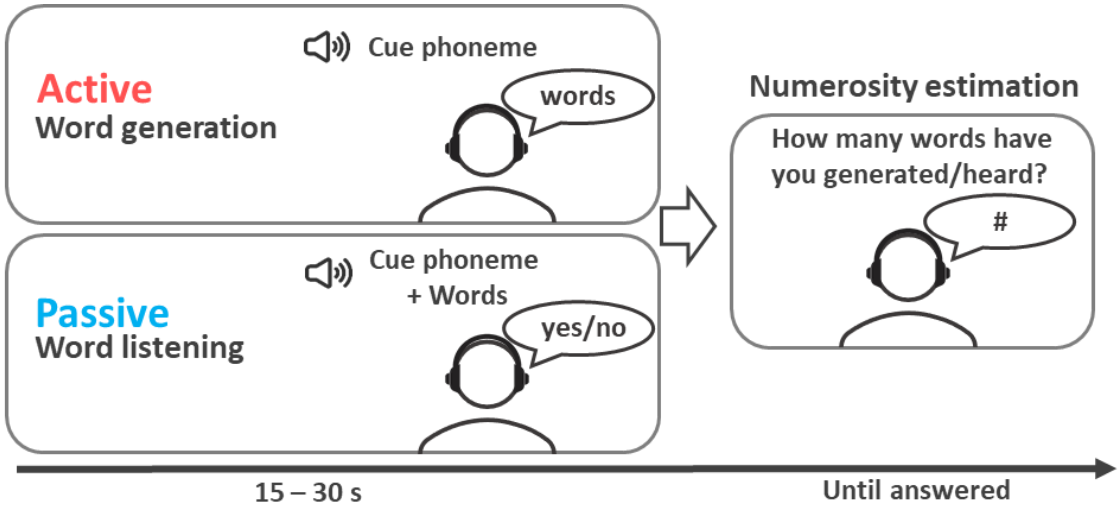

Figure 1. The experimental setup. Schematic representation of the general task flow: active (top) and passive (bottom) conditions consisting of word generation/listening, and numerosity estimation parts. During the active condition participants heard a cue letter and had to generate overtly as many words as possible in a given period of time starting with the cued letter. During the passive condition participants heard a cue letter and a list of words, where they had to answer yes or no for each word whether it contained a cued letter. Auditory stimuli were provided in French.

Stimuli. All the words and phoneme cues were presented to participants as auditory stimuli using Matlab software (mathworks.com). Played back words during the passive condition were chosen from a list of 420 French words (51). Twenty-two cue letters (phonemes) were used randomly for active and passive conditions. The audio stimuli presented during the task were recorded by male and female native French speakers in a neutral manner and registered in wav format with 11025Hz sampling frequency. The gender of the voice pronouncing words in the passive condition matched the participants' gender to avoid possible gender bias.

Procedure. Each condition was repeated three times, and each repetition consisted of 4 trials, resulting in a total of 12 numerosity estimations per condition. The order of repetitions of different experimental conditions was randomized across the experiment and the participants. Before the beginning of the experimental session, participants went through a training session, comprising one repetition of each condition. During the experiment, the participants wore headphones to receive auditory stimuli.

Neuropsychological assessments

Participants included in this study were recruited for a larger TIPP study cohort, where the battery of the neuropsychological assessments was carried out (see more: 52,53). From the available neuropsychological assessments, we focused on executive functioning, as these alterations have been shown to be a prominent feature in psychotic patients (for the review see: 54). The following neuropsychological tests were used to assess executive functions.

1. Initiation and cognitive control were evaluated, employing the semantic verbal fluency (SVF) task for the animal category. The task measures verbal fluency where an individual has to give as many animal names as possible in a one-minute time period without repeating several times the same word or giving proper names. In addition, this task also reflects various executive functions such as self-monitoring, initiation and inhibition, or strategic search of information (55).

2. Working memory was measured using the letter-number sequencing task from WISC III and WAIS III (56,57). During the task, a series of letters-numbers are played and an individual needs to report them back, ordering the letters in alphabetical order and digits in ascending numerical order. This task helps to evaluate the ability to manipulate and update information mentally.

3. Immediate and free recall was assessed with Hopkins Verbal Learning test (58), where participants are asked to immediately recall as many words as possible from a list of 12 words formerly read aloud by the experimenter.

4. Sustained and selective attention was measured using a Continuous Performance Test, identical pairs version (59). During the task, the participant is asked to identify pairs of spatial (shapes) or verbal (numbers) stimuli that are identical in a continuous fashion. This test is associated with distractibility and impulsivity.

The above-mentioned test scores were normalized (z-scored) and combined to obtain a composite score on executive functioning (equation 1) similarly as it was done previously (60). We chose an additional neuropsychological test as a control.

$$\textit{Executive function composite score} = \textit{Immediate and free recall} + \textit{Working memory} + \textit{Mental flexibility and self-monitoring} + \textit{Sustained attention}$$

(Equation 1)

MR image acquisition

MRI data were acquired using a 3 Tesla scanner (Magnetom TrioTim, Siemens Medical Solutions), equipped with a 32-channel head coil. Each MRI session included a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence and a 9- minute gradient echo-planar imaging (EPI) sequence sensitive to BOLD (blood-oxygen-level-dependent) contrast. The MPRAGE acquisition had a 1 mm in-plane resolution and 1.2 mm slice thickness, covering 240 × 257 × 160 voxels (TR = 2.30 ms, TE = 2.98 ms and TI = 900 ms). The functional MRI (EPI) acquisition had isotropic 3.3 mm voxel size, with a 0.3 mm inter-slice gap and covering a total of 64 x 58 x 32 voxels (TR = 1920 ms and TE = 30 ms). Resting-state fMRI (rs-fMRI) was recorded; subjects were lying in the scanner with eyes open, resting but awake and cognitively alert. The acquisition process resulted in a sequence of 280 BOLD images for each participant. Two participants in TI+, four participants in TI- and one participant in CTRL groups were excluded from further imaging analysis due to poor image quality or missing data. Imaging analyses resulted in nineteen patients in the TI+ group, seventeen in TI- and seventeen in CTRL groups.

Functional image preprocessing

Functional data standard pre-processing and analyses were performed using SPM 12 (fil.ion.ucl.ac.uk/spm/) and the functional connectivity toolbox CONN (conn-toolbox.org/) for Matlab (mathworks.com). Functional images were corrected for slice time and motion, co-

registered with a high-resolution anatomical scan, normalized into MNI space, resampled to 1.5 x 1.5 x 1.5 mm3 and smoothed with a 6 mm3 full-width at half maximum (FWHM) Gaussian kernel for each subject. To estimate excessive movement, the mean frame-wise displacement (FD) (61) during the scanning was estimated with the exclusion threshold of 0.5 mm. The groups did not differ in terms of the movements over the scanning period ($F = 2.89$, $p = 0.07$ with the mean FD of 0.18 ± 0.11 mm for TI+, 0.13 ± 0.05 mm for TI- and 0.12 ± 0.04 mm for CTRL groups). Following the standard pipeline for confound removal of the CONN toolbox, the individual time courses of the segmented white matter and cerebrospinal fluid, the six motion parameters with rigid body transformations and their first-order derivatives, and global signal time courses were extracted and regressed out of the data. Regressions were performed for the entire time-series. The BOLD signal data were passed through a band filter (0.009-0.08 Hz). A whole-brain mask in MNI space has restricted data analysis.

Networks

Numerosity network. Numerosity network (Figure 2 A) was based on the previous work in healthy subjects by Stripeikyte et al. (in preparation) where we defined the neural correlates of cognitive self-attenuation during numerosity estimations (for words). The network was derived by comparing connectivity differences in active vs. passive conditions during numerosity estimation when seeding from a major numerosity area, the intraparietal sulcus. The numerosity network included right intraparietal sulcus (IPS; x = 29, y = -65, z = 50), left/ right supplementary motor area (SMA; x = -3, y = -30, z = 63), left superior temporal gyrus (STG; x = -54, y = -20, z = 6) and left inferior parietal lobule (IPL; x = -44, y = -42, z = 29).

Presence hallucination network. Presence hallucination network (PH-network; Figure 2 B) was defined as an overlap of the brain regions associated with the robot-induced PH with the symptomatic PH-network derived from neurological patients experiencing PH (for more details, see Bernasconi, Blondiaux et al., 2020). The overlapping areas of these two experiments were the right posterior middle temporal gyrus (pMTG right; x = 54, y = -54, z = 0), the right inferior frontal gyrus (IFG right; x = 51, y =18, z = 29) and left ventral premotor cortex (vPMC left; x=-26, y=-18, z=57). Those areas were transposed bilaterally.

Control networks. Control regions were derived for Numerosity network and PH-network by shifting each network's regions but keeping the same shape and the same number of voxels

as in the original networks (based on Bernasconi et al., 2020 and Stripeikyte et al., submitted). The areas were shifted to fit in the brain mask and do not comprise of white matter. The Numerosity network areas where shifted by the following coordinates: IPS x-15 y+30 z-15; IPL x y+30 z-15; SMA x y+30 z-15; STG x-15 y+30 z-15. The PH-network areas were shifted following these coordinates: IFG x±20 y+30 z-15; vPMC x±10 y+30 z-15; pMTG x y+30 z-15. A visual network from resting-state fMRI network atlas (62) was analyzed as an additional control network. It was comprised of four regions of interest (ROIs): calcarine sulcus, left thalamus, left and right middle/ superior occipital gyri.

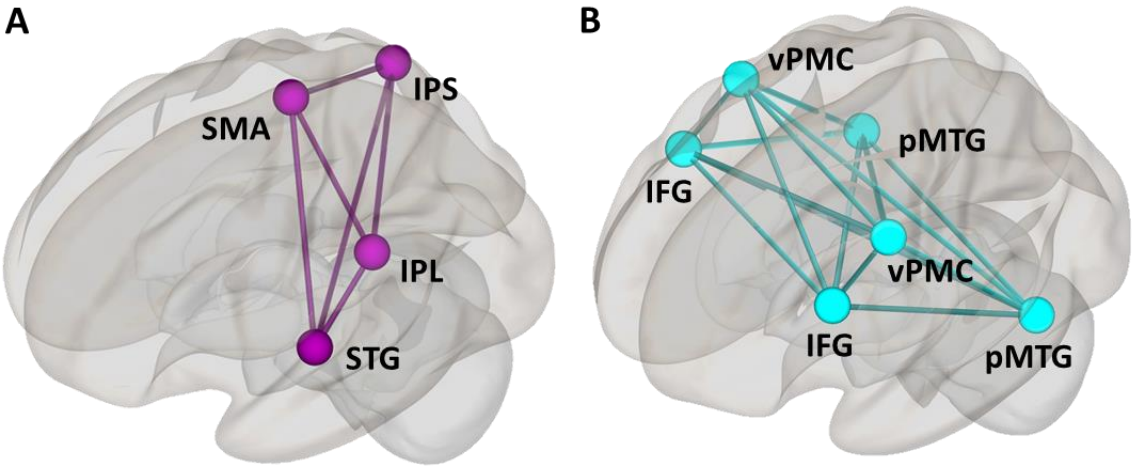

Figure 2. Networks. (A) Projection on the brain surface of 4 regions forming Numerosity network: right intraparietal sulcus (IPS), left supplementary motor area (SMA), left inferior parietal lobule (IPL), left superior temporal gyrus (STG). The network forms 6 connections (lines). Based on Stripeikyte et al., (in preparation). (B) Projection on the brain surface of 6 regions forming PH-network: bilaterally inferior frontal gyrus (IFG), posterior middle temporal gyrus (pMTG), ventral premotor cortex (vPMC). The network forms 15 connections (lines). Based on Bernasconi, Blondiaux et al., 2020.

Statistical analyses

Demographic, psychiatric, and neuropsychological data. Differences in demographic characteristics, clinical and neuropsychological data between the groups were examined by one-way ANOVA analyses looking at the main effect of three groups (psychiatric data was compared only between the patient groups using two-sample t-tests) and a post-hoc pairwise comparisons were performed using R package emmeans (63,64). Pearson's $\chi 2$ tests were performed when applicable.

Number of words generated. First, as a baseline control analysis to indicate the general performance during the phonemic verbal fluency task, we analysed the number of words generated, as it has been shown to be affected in psychotic patients compared to healthy controls (for the review see: 65). The number of words generated (active condition) was analysed applying one-way ANOVA statistics investigating the main effect of Group. Post-hoc pairwise comparisons were performed using R package emmeans (see above) correcting for multiple comparisons with Tukey test (66). The number of words heard (passive condition) was not included into the analyses as it is was fixed by the study design to the mean of 8 words. Education (in years) was included as a covariate of no interest because of significant differences between the groups ($F(1,2) = 10.56$, $p = 0.001$). Trials for which participants did not generate at least 5 words were excluded from behavioral analysis (9 % of all trials). The threshold of 5 words was selected due to the working memory capacity of ~3-5 items (67).

Numerosity performance. To analyze the behavioral task performance during numerosity estimations, we derived the numerosity performance index (45). Numerosity performance is an accuracy ratio reflecting how correctly participants estimated the number of words generated or heard. For each trial, we wanted signed numerosity performance to be proportional to the difference between the reported number of generated/heard words (numerosity estimation) and actually generated/heard number of words. We normalized this difference by the sum of numerosity estimation and actually generated/heard number of words (equation 2) to give more weight to errors made about low numbers of words (i.e., an error of +/- 2 given a numerosity estimation of 8 has higher magnitude than an error of +/-2 given a numerosity estimation of 14). Negative numerosity performance values thus reflected an underestimation of generated/heard words, and positive values reflected an overestimation of generated/heard words. In contrast, null numerosity performance values reflected correct answers about the number of generated/heard words.

$$numerosity\ performance\ = \frac{numerosity\ estimation - words\ generated/heard}{numerosity\ estimation + words\ generated/heard} \text{ (Equation 2)}$$

Numerosity performance was analysed using linear mixed-effects models with Condition (“active”, “passive”) and Group (TI+, TI-, CTRL) as fixed effects and a random intercept by participant. The inclusion of additional random effects was guided by model comparison and

selection based on Bayesian Information Criteria. Education (in years) was included as a covariate of no interest. Analyses were performed using the lme4 (68) and lmerTest (69) packages in R (www.R-project.org). The significance of fixed effects was estimated using Satterthwaite's approximation for degrees of freedom of F statistics (70). Data outliers were removed based on 1.5 IQR from the numerosity performance median value for each participant (9.4 % of all trials were considered as outliers).

fMRI data. Functional connectivity ROI-to-ROI analyses were conducted by extracting bivariate correlation values (Fisher z-transformed) of the Numerosity network and PH-network for all possible connections per network for each participant. Connectivity values were exported and subjected to statistical analysis in R (R-project.org/). Linear mixed-effects models using a Group (TI+, TI-, CTRL) and Connection (6 connections: Numerosity network; 15 connections: PH-network) as fixed effects and Participants as a random effect were applied in order to investigate whether an interaction effect between the groups and all possible connections was present within the Numerosity network or PH-network. Post-hoc analyses with the focus on patients for the between-group differences (TI+ vs. TI-) were performed with FDR (p=0.05) correction for multiple comparisons. The connections which showed significant differences between the patients were also compared against the CTRL group (TI+ vs. CTRL and TI- vs. CTRL) to refine whether the found difference is general for the disease or specific to the presence of TI. Data outliers (6% and 7% of all data points of Numerosity network and PH-network respectively) were removed based on 1.5 IQR from the functional connectivity median value for each connection.

Correlations. Mean numerosity performance of active and passive conditions was correlated with executive function composite score (Spearman correlations) and functional connectivity of affected connections found in ROI-to-ROI analyses (Pearson's correlations).

The results are reported with means ± standard deviations and the range of 95% confidence interval.

3.2.4 Results

Numerosity estimation experiment

Number of words generated. Statistical analysis was only performed for the active condition as the number of words for the passive condition was fixed to the mean of 8 words. Analyses revealed the main effect of Group ($F(2,469) = 16.88$, $p < 0.001$), indicating that there were differences between the groups in number of words generated. Post-hoc analysis revealed that the differences in the active condition, were between the CTRL and either patients group: CTRL ($M = 9.0 \pm 2.1$, CI(95%) = [7.9, 10.1]) generated significantly more words compared to TI+ ($M = 7.4 \pm 1.6$, CI(95%) = [6.6, 8.1]; $t = 5.28$, $p < 0.001$) and compared to TI- ($M = 7.7 \pm 1.7$, CI(95%) = [6.9, 8.5]; $t = 4.26$, $p = 0.001$) groups (Figure 3 A). The patient groups did not differ between each other in the number of words generated ($t = 1.07$, $p = 0.53$). Years of education as a covariate of no interest, did not show a significant effect ($F(1,469) = 0.79$, $p = 0.38$).

Numerosity performance. Numerosity performance was significantly different between conditions (main effect Condition $F(1,1024) = 105$, $p < 0.0001$; active condition $M = -0.04 \pm 0.07$, CI(95%) = [-0.05, -0.01]; passive condition $M = 0.003 \pm 0.07$, CI(95%) = [-0.01, 0.02]), meaning that all participants underestimated more actively generated words compared to the passively generated words (comparable to Stripeikyte et al., in preparation). Specifically, underestimation was observed only during the active condition (t-tests, FDR corrected, all $p < 0.0001$, TI+ $M = -0.04 \pm 0.05$, CI(95%) = [-0.06, -0.01], $t(21) = -6.5$; TI- $M = -0.03 \pm 0.04$, CI(95%) = [-0.07, 0.006], $t(21) = -4.23$; CTRL $M = -0.03 \pm 0.08$, CI(95%) = [-0.07, 0.007], $t(18) = -4.04$), while during the passive condition numerosity performance did not differ from 0 (all $p > 0.07$, Table S1). The interaction of Group x Condition ($F(2,1024) = 3.4$, $p = 0.034$) was significant as well, yet when performing post-hoc contrasts, significant differences surviving multiple corrections were only observed within each group between condition comparisons (Active vs. Passive: TI+ $t(21) = -7.62$, $p < 0.0001$; TI- $t(21) = -5.49$, $p < 0.0001$; CTRL $t(18) = -4.49$, $p < 0.0001$; Figure 3 B , Table S2). No difference emerged between TI+ and the other two groups. Years of education did not influence these data ($F(2,50) = 0.3$, $p = 0.58$).

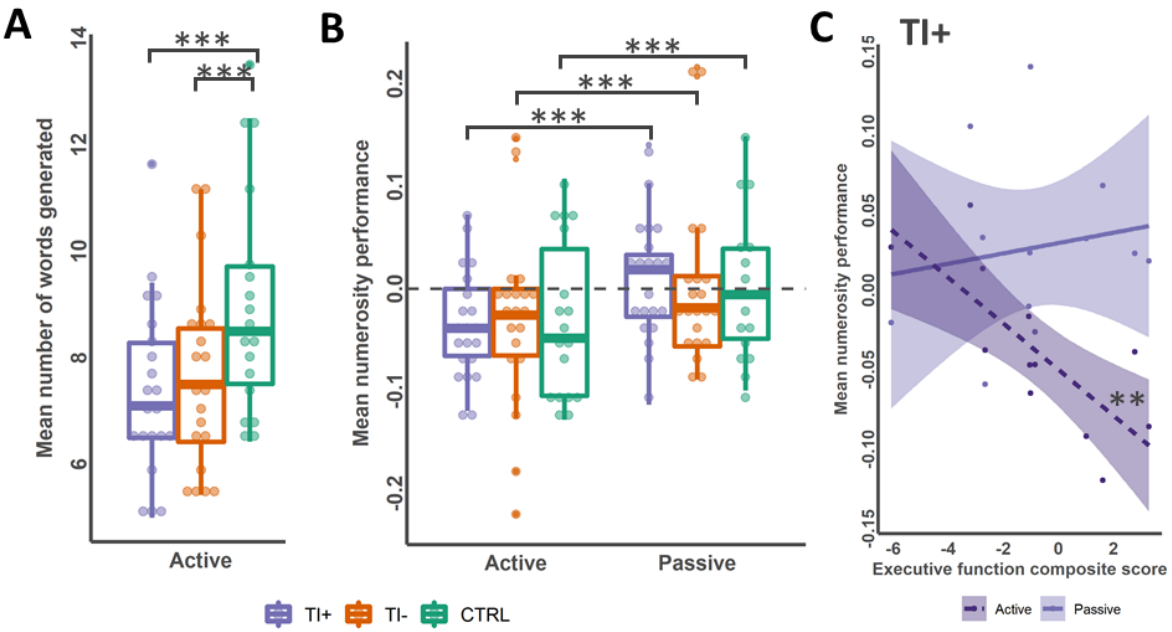

Figure 3. Behavioural results. (A) Mean number of words generated during the active condition respectively for each group (psychotic patients with thought insertion (TI+; violet), psychotic patients without thought insertion (TI-, orange), healthy controls (CTRL, green). (B) Mean numerosity performance during the active and passive conditions for each group. A value of zero represents an ideal numerosity performance. (C) Linear relationship between the mean numerosity performance during the active (dashed line) and passive conditions (straight line) and executive function composite score in TI+ patients. **p<0.01, ***p<0.001. Dots represent individual values of each participant.

Demographic and clinical characteristics

Patient (TI+, TI-) and control (CTRL) groups did not differ in any demographic characteristics (gender, handedness, age; all $p > 0.1$), except for education ($F(2,51) = 10.6$, $p < 0.001$). Patient groups did not differ in clinical characteristics (illness duration, medication dose, PANSS; all $p > 0.2$). The detailed description of demographic and clinical characteristics is represented in Table 1.

Neuropsychological assessments

Regarding the neuropsychological assessments, as expected (54) the CTRL group had higher scores in all cognitive tests assessing executive functions (all $p < 0.04$) and accordingly in the executive function composite score ($p < 0.001$), compared to both groups of psychotic patients. In contrast, patient groups did not differ from each other in neuropsychological

scores assessing executive functions (all p > 0.5). The detailed description of neuropsychological assessments is represented in Table 1.

Correlation analysis revealed a significant negative correlation between mean numerosity performance during the active condition and executive function composite score for TI+ group (rho = -0.825, p = 0.002). As can be seen in Figure 3 C, the lower the TI+ participants executive function score the less underestimation they showed. Moreover, such correlation between frontal executive function and numerosity estimation was absent in the passive condition in the TI+ patients. Moreover, the same analysis in the TI- and CTRL groups did not show a significant relationship between these measures in either the active or the passive conditions (all p>0.1, Table S3, Figure S1).

Characteristic/test	TI+	TI-	CTRL	Main effect	TI+ vs. TI-	TI+ vs. CTRL	TI - vs CTRL
				p (F/chi^2)		p(t/chi^2)	
Group size	21	21	18				
Gender, M/F	13/7	16/3	11/7	0.25 (2.7)	0.2 (1.9)	0.8 (0.1)	0.1 (2.5)
Handedness, R/L	18/1	17/2	16/2	0.79 (0.5)	0.5 (0.4)	0.5 (0.4)	0.9 (<0.0)
Age, y	27.6 ±4.6	24.9 ±4.2	27.3 ±4.9	0.14 (2.0)	0.07 (1.9)	0.8 (0.2)	0.1 (-1.6)
Education, y	11.9 ±1.95	13.7 ±2.6	15.8 ±2.87	<0.001 (10.6)	0.04 (-2.1)	<0.001 (-4.6)	0.01 (-2.5)
Illness duration, y	3.8 ±2.9	2.8 ±2.3	-	-	0.28 (1.1)	-	-
Chlorpromazine, mg/day	348 ±223	311 ±231	-	-	0.63 (0.5)	-	-
PANSS total	60.6 ±15.4	61.4 ±13.8	-	-	0.86 (-0.2)	-	-
PANSS positive	12.9 ±4	12 ±4	-	-	0.49 (0.7)	-	-
PANSS negative	15.4 ±5.7	17.3 ±6.2	-	-	0.33 (-0.9)	-	-
Hopkins Verbal Learning test	24.9 ±4.7	24.4 ±3.7	30.2 ±2.9	<0.001 (12.5)	0.7 (0.3)	0.001 (-4.1)	<0.001 (-4.5)
Letter-number sequences	14.6 ±3.4	15.4 ±3.4	17.7 ±3.1	0.03 (3.8)	0.5 (-0.6)	0.01 (-2.6)	0.04 (-2.1)
Categorical verbal fluency	20.4 ±6.3	21.7 ±5.2	26.7 ±6.8	0.01 (5.1)	0.6 (-0.6)	0.005 (-2.9)	0.02 (-2.5)
Continuous performance test	2.5 ±0.6	2.6 ±0.7	3.2 ±0.6	0.003 (6.6)	0.5 (-0.6)	0.002 (-3.3)	0.007 (-2.8)
Executive function composite score	-0.83±2.7 (NaN = 9)	-1.37±2.5 (NaN = 5)	2.09±2.1	<0.001 (12.3)	0.6 (0.6)	0.001 (-3.7)	<0.001 (-4.6)

Table 1. Demographic, neuropsychological and clinical data of the participants. Data are presented in mean ± standard deviation. ANOVA tests and χ2 tests performed when appropriate. Abbreviations: M – male; F – female; R – right handed; L – left handed; y – years; PANSS – positive and negative symptom scale; TI – thought insertion; CTRL – control; NaN – missing number of subjects for the assessment.

fMRI

Numerosity network. The interaction Group x Connection was significant ($F(10,229) = 2.1$, $p = 0.022$), implying that there are connectivity changes that differed between groups. For the post-hoc analysis we focused on the between patient comparisons, that revealed significant functional connectivity difference between the right IPS and the left IPL when comparing TI+ vs. TI- groups ($r_{TI+} = 0.09 \pm 0.24$, CI(95%) = [-0.02, 0.20]; $r_{TI-} = -0.08 \pm 0.28$, CI(95%) = [-0.23, 0.06]; $t = 2.87$, $p=0.028$; Figure 4). Connectivity between the right IPS and left IPL was increased. None of the other connections differed comparing between the patient groups (all $p > 0.46$, Table S5, Figure S2). Next, we checked whether the observed connectivity alteration between the patient groups is also different between TI+ and CTRL group. We did not observe significant differences between the right IPS and left IPL functional connectivity when comparing TI+ and CTRL ($r_{CTRL} = 0.06 \pm 0.34$, CI(95%) = [-0.11, 0.24]; $t = 0.42$, $p = 0.68$) groups, nor when comparing other connections of numerosity network (all $p > 0.12$, Table S4, Figure S2). There was no significant main effect of Group (TI+ patients $r_{Num\_total} = 0.04 \pm 0.19$, CI(95%) = [0.01, 0.08], TI- patients $r_{Num\_total} = 0.03 \pm 0.22$, CI(95%) = [-0.01, 0.07], CTRL $r_{Num\_total} = 0.02 \pm 0.23$, CI(95%) = [-0.03, 0.07], $F(2,45) = 0.04$, $p = 0.96$), showing that global connectivity in the numerosity network did not differ between the groups. Finally, the main effect of Connection ($F(5,229) = 3.9$, $p = 0.0018$) was significant meaning that the strength of functional connectivity varied between the different connections, independent of group (71).

There were no significant correlations between the mean numerosity performance during the active or passive conditions and right IPS - left IPL functional connectivity for any of the groups (all $p > 0.2$, Table S5).

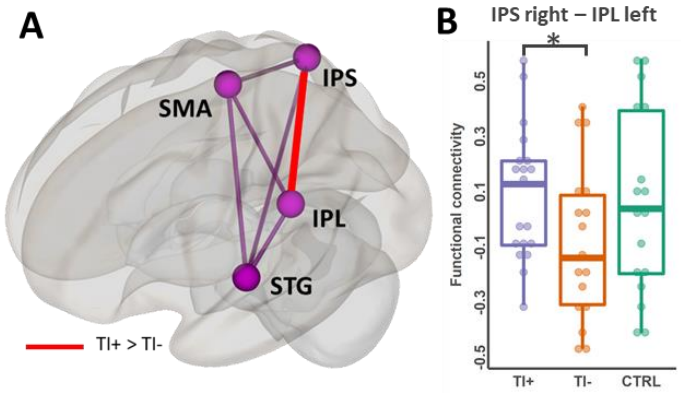

Figure 4. Alterations in numerosity network functional connectivity in psychotic patients with thought insertion (TI+). (A) Abnormal parietal connection is marked in straight red line and was increased in TI+ patients versus TI- patients. (B) Functional connectivity between the right intraparietal sulcus (IPS) and the left inferior parietal lobule (IPL) depicted for each group (psychotic patients with thought insertion (TI+, violet), psychotic patients without thought insertion (TI-, orange), healthy controls (CTRL, green)). Post-hoc FDR corrected at threshold of p=0.05. *p<0.05. Dots represent individual values of each participant.

PH-network. We observed a significant interaction between Group x Connection ($F(28,639) = 3.5$, $p<0.0001$), implying that there are connectivity changes that differed between groups. Post-hoc analysis comparing TI+ vs. TI- groups revealed significant differences in three connections within the PH-network. In more detail, significantly different (reduced) connectivity was found between the right pMTG and the left IFG ($r_{TI+} = 0.03 \pm 0.20$, CI = [-0.07, 0.12]; $r_{TI-} = 0.22 \pm 0.18$, CI(95%) = [0.13, 0.32]; t = -3.04, p=0.019) and between the right and left pMTG ($r_{TI+} = 0.34 \pm 0.27$, CI(95%) = [0.21, 0.48]; $r_{TI-} = 0.55 \pm 0.09$, CI(95%) = [0.49, 0.60]; t = -2.92, p=0.019). Finally, we observed increased frontal connectivity between the left vPMC and the left IFG ($r_{TI+} = 0.33 \pm 0.19$, CI(95%) = [0.24, 0.43]; $r_{TI-} = 0.10 \pm 0.09$, CI(95%) = [0.05, 0.15]; t = 3.40, p=0.011) (Figure 5 A, B). None of the other connections differed between the patient groups (all $p > 0.25$, Table S6, Figure S3).

Next, we assessed whether these three connections, that differed between TI+ and TI- patients, also were significantly different form the CTRL group. We found that connectivity between the right pMTG and the left pMTG ($r_{CTRL} = 0.62 \pm 0.29$, CI(95%) = [0.46, 0.78]; t = -3.3, p=0.008) was significantly reduced and connectivity between the left vPMC and the left IFG ($r_{CTRL} = 0.01 \pm 0.13$, CI(95%) = [-0.06, 0.08]; t = 4.2, p=0.0004) was significantly increased in TI+ patients compared to CTRL. The connectivity between the right pMTG and the left IFG was not significantly different between the TI+ and the CTRL group ($r_{CTRL} = 0.03 \pm 0.22$, CI(95%) =

[-0.10, 0.32]; t = -0.1, p=0.93). See SI for the detailed description of additional disease specific alterations within the PH-network connections between TI+ and CTRL groups that were not observed comparing TI+ and TI- groups. There was no significant main effect of Group, meaning that there was no global difference of PH-network functional connectivity between the groups (TI+ patients r_{PH_total} = 0.25 ± 0.26, CI(95%) = [0.22, 0.28], TI- patients r_{PH_total} = 0.26 ± 0.26, CI(95%) = [0.22, 0.29], CTRL r_{PH_total} = 0.16 ± 0.24, CI(95%) = [0.22, 0.27], F(2,48) = 1.2, p = 0.29). Finally, there was a significant main effect of connection (F(14,640) = 57.3, p<0.0001), meaning that the strength of functional connectivity varied between the different connections of the PH-network, independent of group.

A significant positive correlation was observed in the TI+ group between the mean numerosity performance during the active condition and functional connectivity of the left vPMC and the left IFG and (r = 0.597, p = 0.008; Figure 5 C). No significant correlations were observed for this connection in other groups or with numerosity performance during the passive condition (all p > 0.09, Figure S4, Table S7). See SI for other significant correlations in CTRL group.

Control analyses. The same analyses in control numerosity network shifted regions (main effect of group F(2,50) = 0.9, p = 0.43; group by connection interaction F(2,250) = 1.2 p=0.31; Figure S6), PH-network shifted regions (main effect of group F(2,46) = 0.56, p = 0.57; group by connection interaction F(2,634) = 1.3 p=0.11; Figure S7) and in a visual network (main effect of group F(2,48) = 1.4, p = 0.24; group by connection interaction F(5,161) = 1.8, p=0.06; Figure S8) revealed no significant differences between the tested patient and control groups

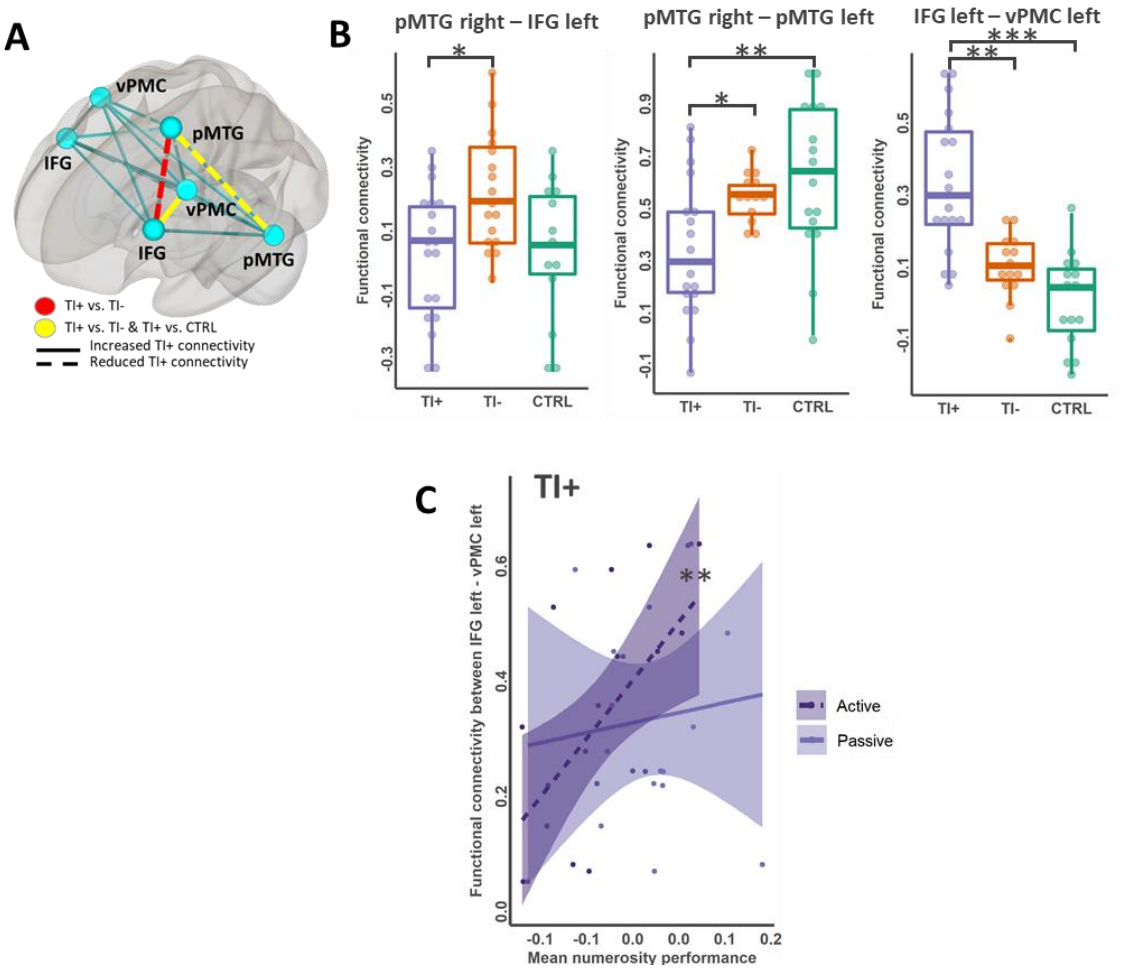

Figure 5. Alterations in the PH-network functional connectivity in psychotic patients with thought insertion (TI+). (A) Abnormal fronto-temporal connections are marked in dashed red line and were decreased in TI+ patients versus TI- patients. Yellow connections mark significant changes in TI+ patients (dashed line decreased connectivity, straight line increased connectivity) compared to TI- and CTRL groups. (B) Functional connectivity between the right posterior middle temporal gyrus (pMTG) and the left inferior frontal gyrus (IFG; left plot), the right pMTG and the left pMTG (middle plot), and the left IFG and left ventral premotor cortex (vPMC, right plot) depicted for each group (psychotic patients with thought insertion (TI+, violet), psychotic patients without thought insertion (TI-, orange), healthy controls (CTRL, green)). Post-hoc FDR corrected at threshold of p=0.05. (C) Linear relationship between the left IFG and left vPMC functional connectivity and mean numerosity performance during the active (dashed line) and passive conditions (straight line) in TI+ patients. *p<0.05 **p<0.01, ***p<0.001. Dots represent individual values of each participant.

3.2.5 Discussion

In the current study, we have combined behavioral and neuroimaging approaches to better understand self-monitoring alterations related to the TI. We have investigated whether the attenuation of self-generated stimuli, an important aspect of self-monitoring, is affected during the cognitive function of numerosity estimations in psychotic patients with TI. We conducted the behavioral experiment where we compared numerosity estimations for self (active condition) and externally (passive condition) generated words. We have shown that self-attenuation can be observed for higher-level cognitive processes such as numerosity estimations and is negatively related to the decreased executive functioning only in TI+ patients. Further, we show functional connectivity increase between the right IPS and left IPL within the numerosity network in TI+ patients.

Additionally, we have investigated the PH-network functional connectivity that accounts for the positive alienation aspect of the symptom. We have observed reduced connectivity between fronto-temporal and temporal areas but increased connectivity between frontal regions within PH-network in TI+ patients. Lastly, we showed that increased connectivity in TI+ patients between left frontal areas within PH-network is positively correlated to the varying levels of cognitive self-attenuation during numerosity estimations. Together, these findings provide a more comprehensive understanding of the behavioral and neural alterations in psychotic TI patients.

Cognitive self-attenuation

In line with our previous study (45), all three (TI+, TI- patients, and CTRL) groups had a general tendency to underestimate the number of words during the active condition. Importantly, this underestimation was significantly different in the active vs. passive conditions, confirming our hypothesis that self-attenuation extends to a higher-level cognitive process. Self-attenuation usually is reported during the sensory processes such as speech (2,72) or arm movement (1,73) and is reflected by dampened behavioral and neural responses of self-generated stimuli compared to externally-generated one (1–3). It is considered that attenuation of self-generated stimuli enables us to distinguish between self and other and perceive stimuli as self-generated (e.g., sense of agency) (74,75). However, this self-other distinction is blurred in psychotic patients (76,77) and indeed, studies report that self-

attenuation is diminished in schizophrenia patients (for the review, see: 6,8). Based on the previous reports of reduced self-attenuation in sensory domains, we expected to observe reduced underestimation in psychotic patients and a more significant reduction in the TI+ group compared to TI- group. Yet, we have not observed significant differences in cognitive self-attenuation between the three groups tested.

There could be several ways to explain the absence of reduced self-attenuation in psychotic patients. First, the experimental setup could be not sensitive enough to detect the differences as it could be a more subtle and complex change in higher-level cognitive processing, giving rise to TI. Second, it is possible that mechanisms causing TI are not linked to reduced self-attenuation reflecting affected self-other distinction. It has been suggested that possible mechanisms for TI could involve abnormal priors (expectations) about the environment and stimuli (see more: 31). Nevertheless, we thought to investigate more thoroughly the first option of a more complex relationship between cognitive self-attenuation and other cognitive functions that are affected in TI+ patients. Affected executive functions such as working memory, attention, fluency are some of the key signs of schizophrenia (for review see: 54). Our task involved the generation of words (phonemic fluency task) where we have observed a reduced number of generated words in psychotic patients compared to controls conforming with the literature. Therefore, of note, to assess the performance during numerosity estimations and be able to perform not biased comparisons between the groups, we normalized the data by the number of words generated/heard. Affected executive functions are especially relevant for TI as in this phenomenon, higher-level processes forming thoughts that do not involve sensory systems such as during auditory verbal hallucinations (auditory areas are affected; 78) are possibly playing a role. We have observed a negative relationship in TI+ patients between numerosity performance during the active condition and executive function composite score. In other words, the more reduced self-attenuation observed during the active condition, the worse executive functioning was found in the TI+ patients. The observed link between the executive functioning and cognitive self-attenuation suggest that the TI phenomenon is related to the deficits in higher-level cognition rather than sensory domains as there exist some suggestions in the literature that TI is a variation of auditory verbal hallucinations and is linked to the altered self-monitoring during inner speech (34–37).

Next, we have investigated functional connectivity within the numerosity network. The numerosity network was defined by examining connectivity differences during the numerosity estimations between the active and passive conditions in healthy volunteers where behavioral cognitive self-attenuation was observed (45). Therefore, it was suggested that the functional connectivity within this network reflects attenuation processing for self-generated stimuli during numerosity estimations. Functional connectivity alterations within this network in TI+ patients could reflect cognitive self-attenuation deficits at the neural level. In more detail, we have observed increased functional connectivity between the right IPS and the left IPL in TI+ patients compared to TI- patients. The right IPS is reported to play a crucial role in numerosity processing (44), while IPL is suggested to account for action monitoring by integrating multisensory information important for self-generated signal distinction (79,80). Increased neural activation of the inferior parietal cortex in psychotic patients with passivity experiences compared to the ones without them have been reported during action monitoring tasks (81–83). These studies suggest that increased activity (insufficient attenuation) of the inferior parietal cortex contributes to the bigger latency to detect incongruency between self and externally generated actions, thus blurring the self-other distinction. Our findings of increased functional connectivity within the numerosity attenuation network between the right IPS and left IPL only in TI+ patients indirectly corroborate the previous results of reduced attenuation at the neural level and extends to the areas involved in numerosity processing.

However, we did not observe significant correlations between the affected functional connectivity within the numerosity network and cognitive self-attenuation in TI+ patients, refraining us from further interpretation about the network's importance to reflect alterations for cognitive self-attenuation in the resting-state fMRI data. To better understand the neural and behavioral underpinnings of cognitive self-attenuation in patients with TI+, future studies should be conducted performing a similar numerosity estimation task during the fMRI acquisition.

Alterations within the PH-network

As our secondary aim of the study, we studied functional connectivity differences within the PH-network that is related to anomalous experiences of an external entity over the self (46,84) and could account for the positive alienation aspect observed in TI+ patients (e.g.,

thoughts generated by someone else). Recently, the study by Serino and colleagues (40) has provided direct evidence that bodily sensorimotor alterations inducing PH, the sensation that somebody is close by when no one is around (85), altered self-monitoring on the cognitive level in healthy volunteers. Thus, we hypothesized that the neural mechanisms accounting for the PH (PH-network; 46) could be affected and related to the cognitive self-monitoring in TI+ patients.

We have observed reduced fronto-temporal functional connectivity within the PH-network in the TI+ group supporting previous proposals of the disconnection hypothesis for hallucinations (86–90) and extending it to the specific network associated with PH. This further corroborates our recent work investigating psychotic patients with and without passivity experiences (90), where the same fronto-temporal connection was found to have reduced functional connectivity in psychotic patients with compared to without passivity experiences. This disconnectivity pattern seems to be specific only to psychotic patients with passivity experiences, including TI, where the external entity over the self is experienced, confirming the relevance of PH and its corresponding neural mechanisms to understand psychotic symptoms (90).

Interestingly, we have found increased functional connectivity in TI+ patients between the left IFG and the left vPMC areas within the PH-network. This difference was not observed in psychotic patients with passivity experiences (90), suggesting the alteration specificity, particularly to the TI. The lateral prefrontal cortex (involving IFG) and premotor regions, considered as crucial areas for information processing and cognitive control, are often reported to be affected in psychotic patients (91,92) and are linked with disorganized cognitive functioning (93–95). It is then plausible that increased connectivity between the left frontal PH-network areas reflects altered cognitive functioning. This idea was strengthened by looking at the relationship between cognitive self-attenuation and affected PH-network functional connectivity in TI+ patients. We found a positive correlation between increasing functional connectivity of the left frontal connection within the PH-network and reducing cognitive self-attenuation for TI+ patients only. The relationship between other altered connections (fronto-temporal, temporal) in TI+ patients and cognitive self-attenuation was not observed. These findings suggest the subtle relationship of cognitive self-attenuation to altered cognitive control reflected in increased connectivity of frontal areas, which are also

involved in the occurrence of PH. This finding further strengthens the proposition that TI is related to cognitive self-monitoring dysfunction.

Conclusions

To sum up, we showed a relationship between the altered cognitive functioning and self-attenuation during numerosity estimations in TI+ patients. We also revealed altered functional connectivity in TI+ patients within the areas involved in the attenuation processing during numerosity estimations and PH-network related to the alienation aspect of the symptom. The observed functional connectivity changes were specific only to the psychotic TI+ patients, suggesting the specificity of alterations associated with self-monitoring when the self is misattributed to an external entity. These deficits could play a role in blurring the attribution of self during cognitive processes, linking TI to the insufficient self-monitoring over cognitive processes.

3.2.6 References

1. Shergill SS, White TP, Joyce DW, Bays PM, Wolpert DM, Frith CD. Modulation of somatosensory processing by action. Neuroimage. 2013;70:356–62.

2. Timm J, SanMiguel I, Keil J, Schröger E, Schönwiesner M. Motor Intention Determines Sensory Attenuation of Brain Responses to Self-initiated Sounds. J Cogn Neurosci. 2014 Jul;26(7):1481–9.

3. Benazet M, Thénault F, Whittingstall K, Bernier PM. Attenuation of visual reafferent signals in the parietal cortex during voluntary movement. J Neurophysiol. 2016;116(4):1831–9.

4. Scott M. Corollary Discharge Provides the Sensory Content of Inner Speech. Psychol Sci. 2013;24(9):1824–30.

5. Bays PM, Flanagan JR, Wolpert DM. Attenuation of self-generated tactile sensations is predictive, not postdictive. PLoS Biol. 2006;4(2):281–4.

6. Whitford TJ. Speaking-Induced Suppression of the Auditory Cortex in Humans and Its Relevance to Schizophrenia. Biol Psychiatry Cogn Neurosci Neuroimaging. 2019;4(9):791–804.

7. Brooks JX, Cullen KE. Predictive Sensing: The Role of Motor Signals in Sensory Processing. Biol Psychiatry Cogn Neurosci Neuroimaging. 2019;4(9):842–50.

8. Bansal S, Ford JM, Spering M. The function and failure of sensory predictions. Ann N Y Acad Sci. 2018;1426(1):199–220.

9. Blakemore SJ, Smith J, Steel R, Johnstone CE, Frith CD. The perception of self-produced sensory stimuli in patients with auditory hallucinations and passivity experiences: evidence for a breakdown in self-monitoring. Psychol Med. 2000;30(5):1131–9.

10. Blakemore SJ, Frith CD, Wolpert DM. Spatio-temporal prediction modulates the perception of self-produced stimuli. J Cogn Neurosci. 1999;11(5):551–9.

11. Frith C. Explaining delusions of control: The comparator model 20years on. Conscious Cogn. 2012;21(1):52–4.

12. Waters F, Jablensky A. Time discrimination deficits in schizophrenia patients with first-rank (passivity) symptoms. Psychiatry Res. 2009;167(1–2):12–20.

13. Wolpert DM, Flanagan JR. Motor prediction. Curr Biol. 2001;11(18):729–32.

14. Feinberg I. Efference copy and corollary discharge: implications for thinking and its disorders. Schizophr Bull. 1978;4(4):636–40.

15. Frith C. Neuropsychology of Schizophrenia. In: British Medicall Bulletin. London: Springer Berlin Heidelberg; 1996. p. 618–26.

16. Frith CD. Can a Problem With Corollary Discharge Explain the Symptoms of Schizophrenia? Biol Psychiatry Cogn Neurosci Neuroimaging. 2019;4(9):768–9.

17. Schneider K. [Primary & secondary symptoms in schizophrenia]. Fortschr Neurol Psychiatr Grenzgeb. 1957 Sep;25(9):487–90.

18. Salomon R, Progin P, Griffa A, Rognini G, Do KQ, Conus P, et al. Sensorimotor Induction of Auditory Misattribution in Early Psychosis. Schizophr Bull. 2020 Feb 11;1–8.

19. Graham-Schmidt KT, Martin-Iverson MT, Waters FAV. Self- and other-agency in people with passivity (first rank) symptoms in schizophrenia. Schizophr Res. 2018;192:75–81

20. Waters FAV, Badcock JC, Dragović M, Jablensky A. Neuropsychological functioning in schizophrenia patients with first-rank (passivity) symptoms. Psychopathology. 2009;42(1):47–58.

21. Ford JM, Mathalon DH. Efference Copy, Corollary Discharge, Predictive Coding, and Psychosis. Biol Psychiatry Cogn Neurosci Neuroimaging. 2019;4(9):764–7.

22. Ford JM, Palzes VA, Roach BJ, Mathalon DH. Did I Do That? Abnormal Predictive Processes in Schizophrenia When Button Pressing to Deliver a Tone. Schizophr Bull. 2014 Jul;40(4):804–12.

23. Pynn LK, DeSouza JFX. The function of efference copy signals: Implications for symptoms of schizophrenia. Vision Res. 2013;76:124–33.

24. Shergill SS, Samson G, Bays PM, Frith CD, Wolpert DM. Evidence for sensory prediction deficits in schizophrenia. Am J Psychiatry. 2005;162(12):2384–6.

25. Shergill SS, White TP, Joyce DW, Bays PM, Wolpert DM, Frith CD. Functional magnetic resonance imaging of impaired sensory prediction in schizophrenia. JAMA Psychiatry. 2014;71(1):28–35.

26. WHO ICD-10. International statistical classification of diseases and related health problems, 10th revision (ICD-10). World Heal Organ. 2016;1(Chapter V):332–45.

27. Mullins S, Spence S a. Re-examining thought insertion: Semi-structured literature review and conceptual analysis. Br J Psychiatry. 2014;182:293–8.

28. Schneider K. Clinical psychopathology. Grune & Stratton; 1959.

29. Vosgerau G, Newen A. Thoughts, motor actions, and the self. Mind Lang. 2007;22(1):22–43.

30. Martin JR, Pacherie E. Out of nowhere: Thought insertion, ownership and context-integration. Conscious Cogn. 2013;22(1):111–22.

31. Sterzer P, Mishara AL, Voss M, Heinz A. Thought Insertion as a Self-Disturbance: An Integration of Predictive Coding and Phenomenological Approaches. Front Hum Neurosci. 2016;10(October):1–12.

32. Doshi R, Christoff K. Introduction: The cognitive neuroscience of thought. Brain Res. 2012;1428:1–2.

33. Marupaka N, Iyer LR, Minai AA. Connectivity and thought: The influence of semantic network structure in a neurodynamical model of thinking. Neural Networks. 2012;32:147–58.

34. Jones SR, Fernyhough C. Thought as action: Inner speech, self-monitoring, and auditory verbal hallucinations. Conscious Cogn. 2007;16(2):391–9.

35. Langland-Hassan P. Fractured phenomenologies: Thought insertion, inner speech, and the puzzle of extraneity. Mind Lang. 2008;23(4):369–401.

36. Vicente A. The comparator account on thought insertion, alien voices and inner speech: Some open questions. Phenomenol Cogn Sci. 2014;13(2):335–53.

37. Wilkinson S, Alderson-Day B. Voices and Thoughts in Psychosis: An Introduction. Rev Philos Psychol. 2016;7(3):529–40.

38. Sartorius N, Jablensky A, Korten A, Ernberg G, Anker M, Cooper JE, et al. Early manifestations and first-contact incidence of schizophrenia in different cultures: A preliminary report on the initial evaluation phase of the WHO Collaborative Study on Determinants of Outcome of Severe Mental Disorders. Psychol Med. 1986 Nov 9;16(4):909–28.

39. Thorup A, Petersen L, Jeppesen P, Nordentoft M. Frequency and predictive values of first rank symptoms at baseline among 362 young adult patients with first-episode schizophrenia. Results from the Danish OPUS study. Schizophr Res. 2007;97(1–3):60–7.

40. Serino A, Pozeg P, Bernasconi F, Solcà M, Hara M, Progin P, Stripeikyte S, et al. Thought consciousness and source monitoring depend on robotically-controlled sensorimotor conflicts and illusory states. *In revision* for iScience.

41. Olson JA, Landry M, Appourchaux K, Raz A. Simulated thought insertion: Influencing the sense of agency using deception and magic. Conscious Cogn. 2016;43:11–26.

42. Walsh E, Oakley DA, Halligan PW, Mehta MA, Deeley Q. Brain mechanisms for loss of awareness of thought and movement. Soc Cogn Affect Neurosci. 2017;12(5):793–801.

43. Dehaene S. The Number Sense. Oxford Univ. Press; 1997.

44. Arsalidou M, Taylor MJ. Is 2+2=4? Meta-analyses of brain areas needed for numbers and calculations. Neuroimage. 2011;54(3):2382–93.

45. Stripeikyte G, Pereira M, Rognini G, Potheegadoo J, Faivre N, Blanke O. Cognitive self-attenuation during word numerosity estimations. *In preparation*.

46. Bernasconi F, Blondiaux E, Potheegadoo J, Stripeikyte G, Pagonabarraga J, Bejr-Kasem H, et al. Sensorimotor hallucinations in Parkinson' s disease. bioRxiv. 2020;

47. Baumann PS, Crespi S, Marion-Veyron R, Solida A, Thonney J, Favrod J, et al. Treatment and early intervention in psychosis program (TIPP-Lausanne): Implementation of an early intervention programme for psychosis in Switzerland. Early Interv Psychiatry. 2013;7(3):322–8.

48. Andreasen NC. Scale for the Assessment of Positive Symptoms (SAPS). Br J Psychiatry Suppl. 1984;(7):49–58.

49. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261–76.

50. Lezak MD. Neuropsychological assessment (3rd ed.). Neuropsychological assessment (3rd ed.). 1995. 544–546 p.

51. Ferrand L, Alario F-X. Normes d'associations verbales pour 366 noms d'objets concrets. Annee Psychol. 1998;98(4):659–709.

52. Alameda L, Fournier M, Khadimallah I, Griffa A, Cleusix M, Jenni R, et al. Redox dysregulation as a link between childhood trauma and psychopathological and neurocognitive profile in patients with early psychosis. Proc Natl Acad Sci U S A. 2018;115(49):12495–500.

53. Conus P, Seidman LJ, Fournier M, Xin L, Cleusix M, Baumann PS, et al. N-acetylcysteine in a double-blind randomized placebo-controlled trial: Toward biomarker-guided treatment in early psychosis. Schizophr Bull. 2018;44(2):317–27.

54. Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraone S V., Seidman LJ. Neurocognition in First-Episode Schizophrenia: A Meta-Analytic Review. Neuropsychology. 2009;23(3):315–36.

55. Cardebat D, Démonet JF, Viallard G, Faure S, Puel M, Celsis P. Brain Functional Profiles in Formal and Semantic Fluency Tasks: A SPECT Study in Normals. Brain Lang. 1996 Feb;52(2):305–313.

56. Wechsler D. Wechsler adult intelligence scale-III: administration and scoring manual. Psychologi. San Antonio; 1997.

57. Wechsler D. The Wechsler intelligence scale for children—third edition: administration and scoring manual. Psychologi. San Antonio; 1991.

58. Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins verbal learning test - Revised: Normative data and analysis of inter-form and test-retest reliability. Clin Neuropsychol. 1998;12(1):43–55.

59. Cornblatt BA, Risch NJ, Faris G, Friedman D, Erlenmeyer-Kimling L. The continuous performance test, identical pairs version (CPT-IP): I. new findings about sustained attention in normal families. Psychiatry Res. 1988;26(2):223–38.

60. Pagonabarraga J, Kulisevsky J, Llebaria G, García-Sánchez C, Pascual-Sedano B, Gironell A. Parkinson's disease-cognitive rating scale: A new cognitive scale specific for Parkinson's disease. Mov Disord. 2008;23(7):998–1005.

61. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage. 2012;59(3):2142–54.

62. Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD. Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cereb Cortex. 2012;22(1):158–65.

63. Lenth R, Singmann H, Love J, Buerkner P, Herve M. emmeans: Estimated Marginal Means, aka Least-Squares Means. R package version 1.15-15. 2020.

64. Searle SR, Speed FM, Milliken GA. Population Marginal Means in the Linear Model: An Alternative to Least Squares Means. Am Stat. 1980;

65. Henry JD, Crawford JR. A meta-analytic review of verbal fluency deficits in schizophrenia relative to other neurocognitive deficits. Cogn Neuropsychiatry. 2005;10(1):1–33.

66. Tukey JW. Comparing Individual Means in the Analysis of Variance. Biometrics. 1949;5(2):99.

67. Cowan N. The magical mystery four: How is working memory capacity limited, and why? Curr Dir Psychol Sci. 2010;19(1):51–7.

68. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4 | Bates | Journal of Statistical Software. J Stat Softw. 2015;67(1).

69. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest Package: Tests in Linear Mixed Effects Models . J Stat Softw. 2017;82(13).

70. Luke SG. Evaluating significance in linear mixed-effects models in R. Behav Res Methods. 2017;49(4):1494–502.

71. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007;8(9):700–11.

72. Baess P, Horváth J, Jacobsen T, Schröger E. Selective suppression of self-initiated sounds in an auditory stream: An ERP study. Psychophysiology. 2011;48(9):1276–83.

73. Kilteni K, Ehrsson HH. Functional connectivity between the cerebellum and somatosensory areas implements the attenuation of self-generated touch. J Neurosci. 2019 Dec 6;1732–19.

74. Weiss C, Herwig A, Schütz-Bosbach S. The self in action effects: Selective attenuation of self-generated sounds. Cognition. 2011;121(2):207–18.

75. Blakemore SJ, Wolpert D, Frith C. Why can't you tickle yourself? Neuroreport. 2000;11(11):R11–6.

76. Frith CD, Blakemore SJ, Wolpert DM. Explaining the symptoms of schizophrenia: Abnormalities in the awareness of action. Brain Res Rev. 2000;31(2–3):357–63.

77. van der Weiden A, Prikken M, van Haren NEM. Self-other integration and distinction in schizophrenia: A theoretical analysis and a review of the evidence. Neurosci Biobehav Rev. 2015;57:220–37.

78. Cho R, Wu W. Mechanisms of auditory verbal hallucination in schizophrenia. Front Psychiatry. 2013;4(NOV):1–8.

79. Rizzolatti G, Ferrari PF, Rozzi S, Fogassi L. The inferior parietal lobule: Where action becomes perception. In: Percept, Decision, Action: Bridging the Gaps. 2008. p. 129–45.

80. Gerrans P. The feeling of thinking: Sense of agency in delusions of thought insertion. Psychol Conscious Theory, Res Pract. 2015;2(3):291–300.

81. Farrer C, Franck N, Frith CD, Decety J, Georgieff N, D'Amato T, et al. Neural correlates of action attribution in schizophrenia. Psychiatry Res Neuroimaging. 2004 May;131(1):31–44.

82. Schnell K, Heekeren K, Daumann J, Schnell T, Schnitker R, Möller-Hartmann W, et al. Correlation of passivity symptoms and dysfunctional visuomotor action monitoring in psychosis. Brain. 2008;131(10):2783–97.

83. Spence SA, Brooks DJ, Hirsch SR, Liddle PF, Meehan J, Grasby PM. A PET study of voluntary movement in schizophrenic patients experiencing passivity phenomena (delusions of alien control). Brain. 1997;120(11):1997–2011.

84. Blanke O, Pozeg P, Hara M, Heydrich L, Serino A, Yamamoto A, et al. Neurological and robot-controlled induction of an apparition. Curr Biol. 2014;24(22):2681–6.

85. Jaspers K. Über leibhaftige Bewusstheiten (Bewusstheitstaüschungen), ein psychopathologisches Elementarsymptom. Zeitschrift für Pathopsychologie. 1913;2:150–61.

86. Crossley N a., Mechelli A, Fusar-Poli P, Broome MR, Matthiasson P, Johns LC, et al. Superior temporal lobe dysfunction and frontotemporal dysconnectivity in subjects at risk of psychosis and in first-episode psychosis. Hum Brain Mapp. 2009;30(12):4129–37.

87. Karbasforoushan H, Woodward ND. Resting-State Networks in Schizophrenia. Curr Top Med Chem. 2013;12(21):2404–14.

88. Oertel-Knöchel V, Knöchel C, Matura S, Stäblein M, Prvulovic D, Maurer K, et al. Association between symptoms of psychosis and reduced functional connectivity of auditory cortex. Schizophr Res. 2014;160(1–3):35–42.

89. Skudlarski P, Jagannathan K, Anderson K, Stevens MC, Calhoun VD, Skudlarska BA, et al. Brain Connectivity Is Not Only Lower but Different in Schizophrenia: A Combined Anatomical and Functional Approach. Biol Psychiatry. 2010;68(1):61–9.

90. Stripeikyte G, Potheegadoo J, Progin P, Blondiaux E, Do KQ, Conus P, et al. Fronto-temporal disconnection within the presence hallucination network in psychotic patients with passivity experiences. *Submitted to Schz Bull*.

91. He Y, Wu S, Chen C, Fan L, Li K, Wang H, et al. Organized resting - state functional dysconnectivity of the prefrontal cortex in patients with schizophrenia. Neuroscience. 2020.

92. Barbalat G, Chambon V, Franck N, Koechlin E, Farrer C. Organization of cognitive control within the lateral prefrontal cortex in schizophrenia. Arch Gen Psychiatry. 2009;66(4):377–86.

93. Lesh TA, Niendam TA, Minzenberg MJ, Carter CS. Cognitive control deficits in schizophrenia: Mechanisms and meaning. Neuropsychopharmacology. 2011;36(1):316–38.

94. Yoon JH, Minzenberg MJ, Ursu S, Walters R, Wendelken C, Ragland JD, et al. Association of dorsolateral prefrontal cortex dysfunction with disrupted coordinated brain activity in schizophrenia: Relationship with impaired cognition, behavioral disorganization, and global function. Am J Psychiatry. 2008;165(8):1006–14.

95. Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch Gen Psychiatry. 2009;66(8):811–22.

3.2.7 Supplementary Information

ROI-to-ROI analysis

PH-network. Linear mixed model analyses were performed for the PH-network investigation (all connections' functional connectivity is depicted in Figure S3). Post-hoc analyses comparing between the groups, have showed several connections which were different between the TI+ and CTRL groups. Specifically, TI+ patients compared to CTRL group had increased functional connectivity between the right IFG and left vPMC (r_{TI+} = 0.22 ± 0.16, CI(95%) = [-0.14, 0.30]; r_{CTRL} = -0.01 ± 0.19, CI(95%) = [-0.11, 0.09]; t = 2.93, p=0.014) and the left pMTG and left vPMC (r_{TI+} = 0.17 ± 0.15, CI(95%) = [0.09, 0.24]; r_{CTRL} = -0.06 ± 0.15, CI(95%) = [-0.14, 0.02]; t = 2.91, p = 0.014).

Correlation analyses between mean numerosity performance and affected connections in TI+ group within PH-network have revealed additional findings to the main reported results. We have also observed significant positive correlations in the CTRL group between the mean numerosity performance during the active and passive conditions, and functional connectivity of the right pMTG and the left pMTG (active r = 0.595, p = 0.01; passive r = 0.603, p = 0.01; Figure S5, Table S8).

Control networks. Control networks' functional connectivity in patients with psychosis were analyzed applying the same analysis as reported in the methods section. The PH-network shifter regions and visual network were used the same as in our previous study by Stripeikyte et al., (*submitted*).

Shifted numerosity attenuation network regions were derived as follow: right IPS x-15 y+30 z-15 -> right supramarginal gyrus (SMG); left IPL x y+30 z-15 -> left opercular inferior frontal gyrus (opIFG); left/right SMA x y+30 z-15 -> left medial superior frontal gyrus (mSFG); left STG x-15 y+30 z-15 -> left orbital inferior frontal gyrus (oIFG). Linear mixed model analysis revealed no significant effect of group (F(2,50) = 0.86, p = 0.43; TI+ r_total = 0.08 ± 0.23, CI(95%) = [0.03, 0.12]; TI- r_total = 0.07 ± 0.22, CI(95%) = [0.03, 0.12]; CTRL r_total = 0.04 ± 0.23, CI(95%) = [-0.003, 0.09], Figure S6) nor interaction of group and connection (F(2,250) = 1.2 p=0.31). Main effect connections (F(5,250) = 26.8, p<0.0001) was significant.

Statistical analysis in control shifted PH-network regions showed no significant effect of group (F(2,46) = 0.56, p = 0.57; TI+ r_total = 0.08 ± 0.38, CI(95%) = [0.04, 0.13]; TI- r_total = 0.07 ± 0.34, CI(95%) = [0.02, 0.11]; CTRL r_total = 0.09 ± 0.34, CI(95%) = [0.05, 0.14], Figure S7) nor interaction of group and connection (F(2,634) = 1.3 p=0.11). Main effect connections (F(14,634) = 79.6, p<0.0001) was significant.

Visual network from resting state fMRI network atlas (Shirer et al., 2012) was analyzed as a second control. Statistical analysis in the visual network showed no significant effect of group (F(2,48) = 1.4, p = 0.24; TI+ r_total = 0.39 ± 0.43, CI(95%) = [0.31, 0.47]; TI- r_total = 0.33 ± 0.44, CI(95%) = [0.24, 0.42] ; CTRL r_total = 0.33 ± 0.45, CI(95%) = [0.25, 0.42], Figure S8) and group by connection interaction (F(5,161) = 1.8, p=0.06). Main effect connections (F(5,245) = 312.5, p < 0.001) were significant.

Supplementary figures

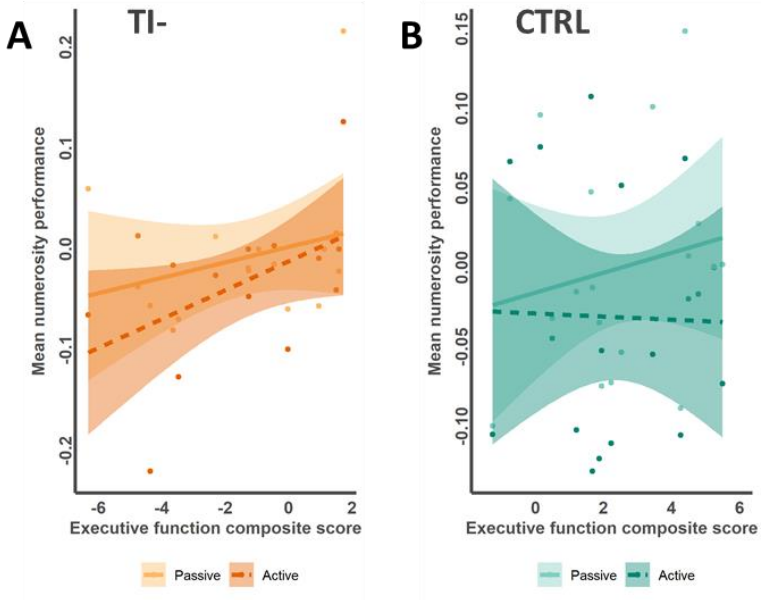

Figure S1. Correlations between mean numerosity performance and executive function composite score. Spearman correlations between the mean numerosity performance during the active (dashed line) and passive conditions (straight line) and executive function composite score in (A) psychotic patients without thought insertion (TI-, orange), (B) healthy controls (CTRL, green). No significant relationships were observed. Dots represent individual values of each participant.

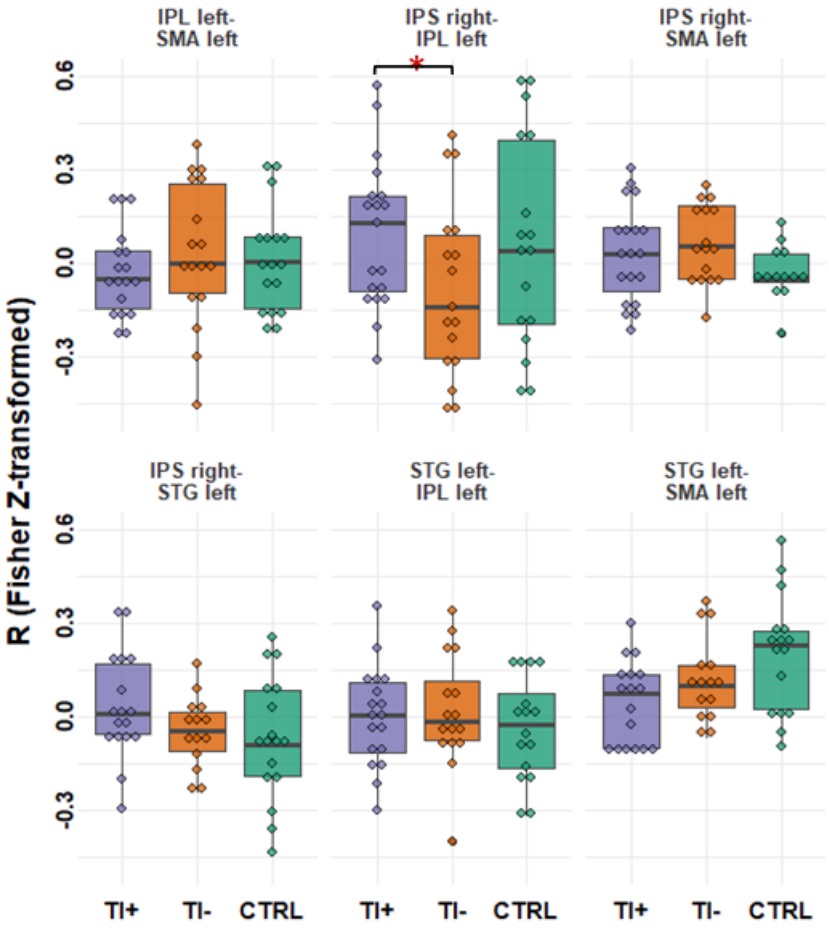

Figure S2. Functional connectivity of 6 numerosity network connections. IPS – intraparietal sulcus, IPL- inferior parietal lobule, SMA – supplementary motor area, STG – superior temporal gyrus. Post-hoc FDR corrected at threshold of p=0.05. *p<0.05. Dots represent individual values of each participant.

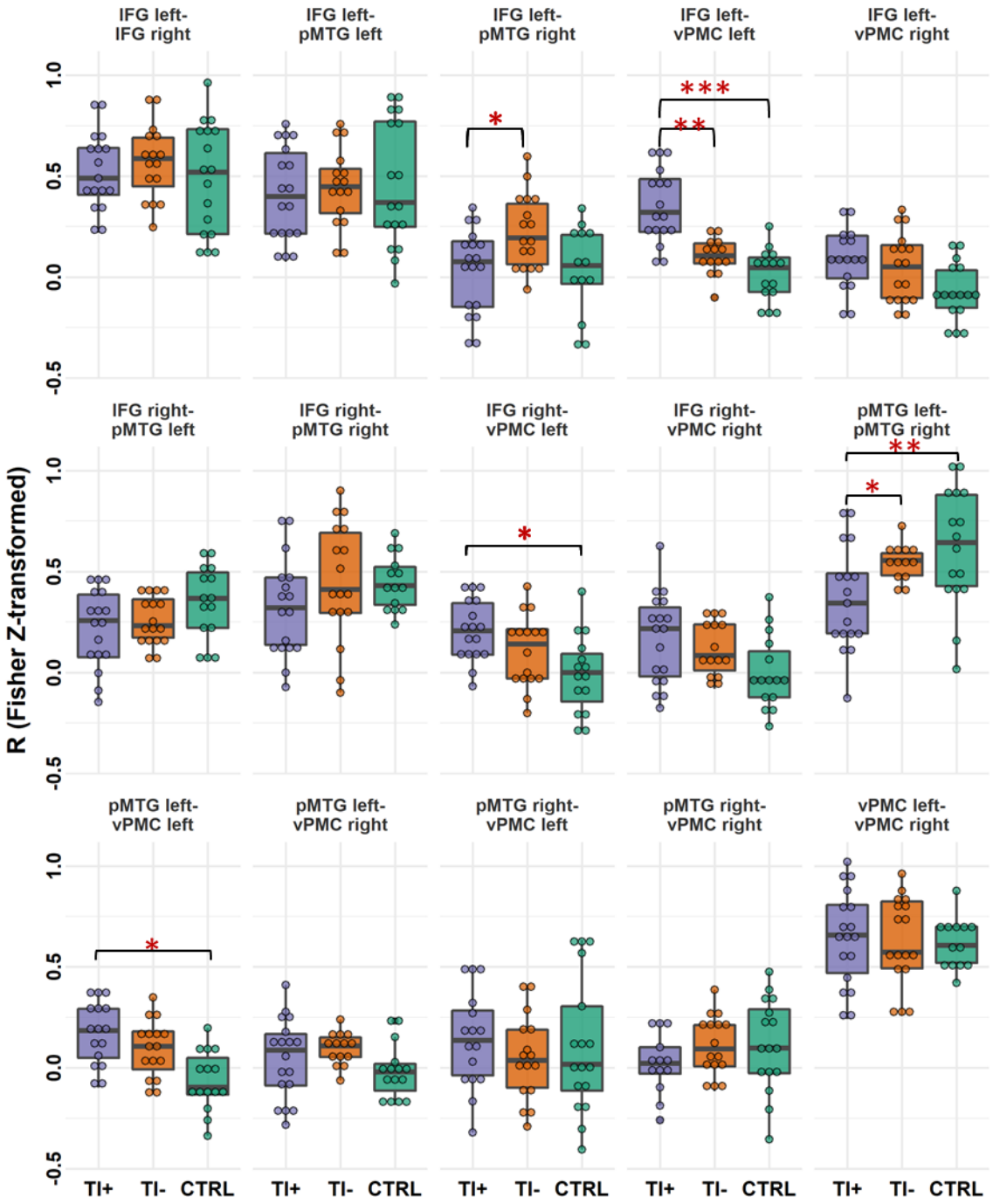

Figure S3. Functional connectivity of 15 PH-network connections. IFG - inferior frontal gyrus, pMTG - posterior middle temporal gyrus, vPMC - ventral premotor cortex. Post-hoc FDR corrected at threshold of p=0.05. *p<0.05 **p<0.01, ***p<0.001. Dots represent individual values of each participant.

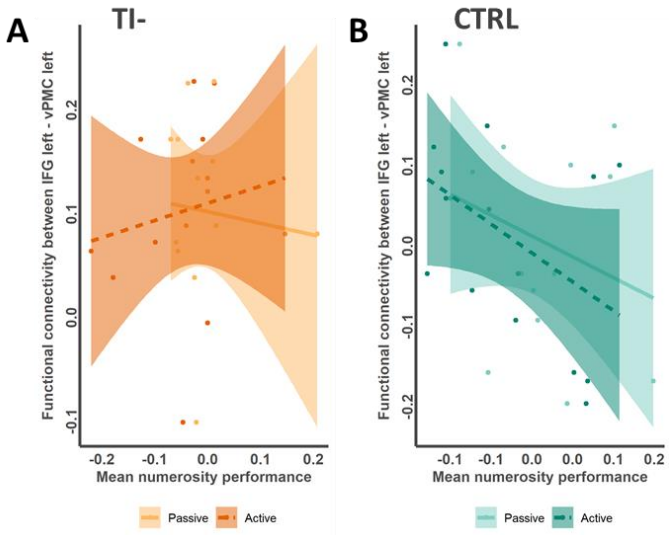

Figure S4. Correlations between mean numerosity performance and functional connectivity between the left IFG and left vPMC. Pearson correlations between the mean numerosity performance during the active (dashed line) and passive conditions (straight line) and functional connectivity of PH-network connection between the left inferior frontal gyrus (IFG) and the left ventral premotor cortex (vPMC) in (A) psychotic patients without thought insertion (TI-, orange), (B) healthy controls (CTRL, green). No significant relationships were observed. Dots represent individual values of each participant.

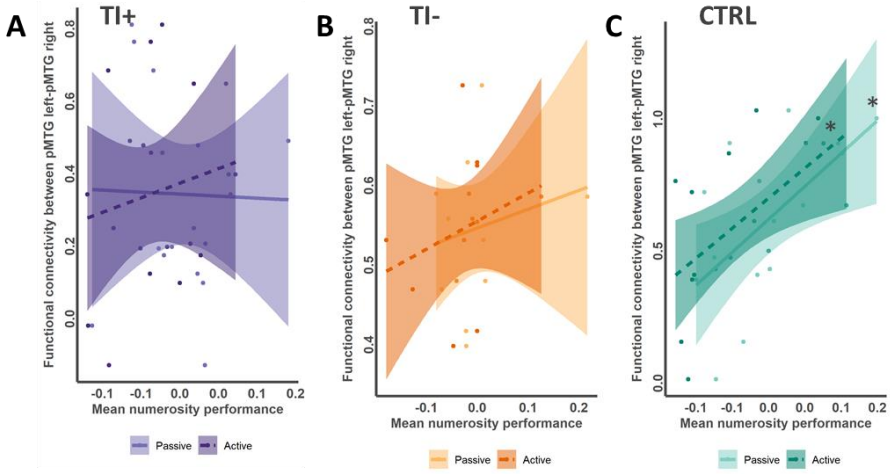

Figure S5. Correlations between mean numerosity performance and functional connectivity between the left pMTG and right pMTG. Pearson correlations between the mean numerosity performance during the active (dashed line) and passive conditions (straight line) and functional connectivity of PH-network connection between the left and right posterior middle temporal gyrus (pMTG) in (A) psychotic patients with thought insertion (TI-, purple), (B) psychotic patients without thought insertion (TI-, orange) (C) healthy controls (CTRL, green). No significant relationships were observed. *p<0.05. Dots represent individual values of each participant.

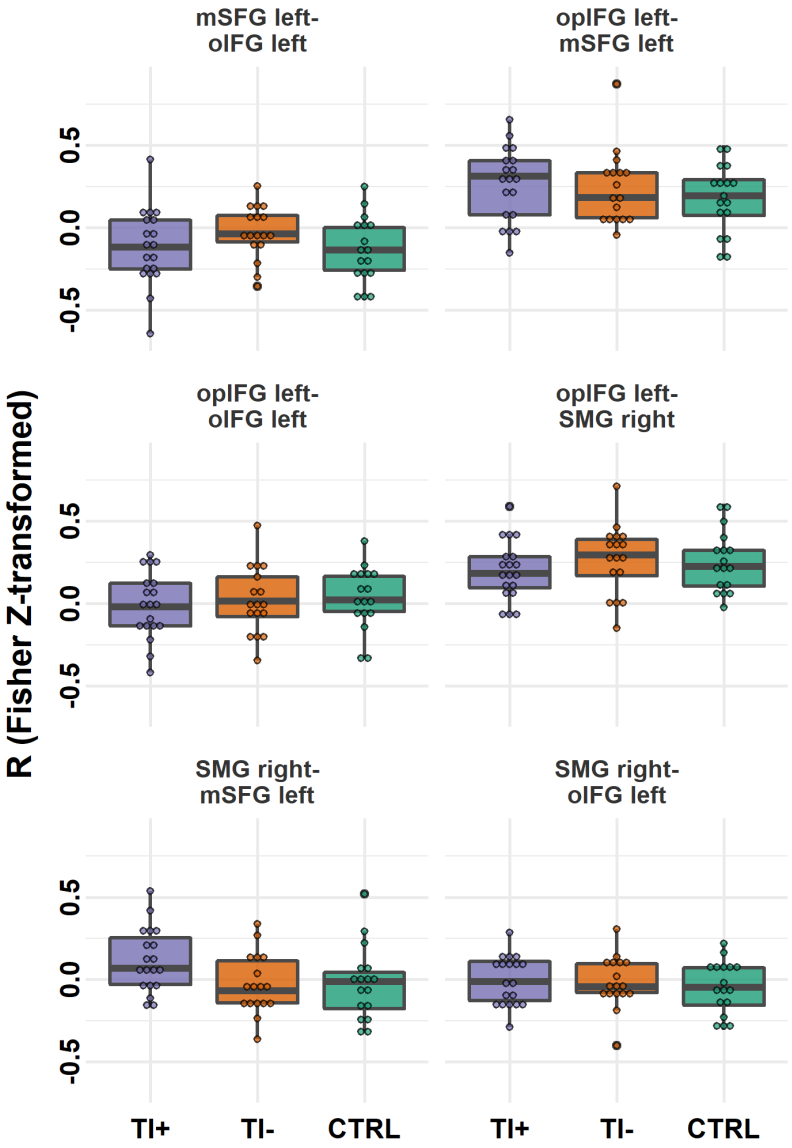

Figure S6. Functional connectivity of 6 control shifted Numerosity attenuation network region connections. No significant differences between the groups were observed. mSFG – medial superior frontal gyrus, oIFG – orbital inferior frontal gyrus, opIFG – opercular inferior frontal gyrus, SMG – supramarginal gyrus. Dots represent individual values of each participant.

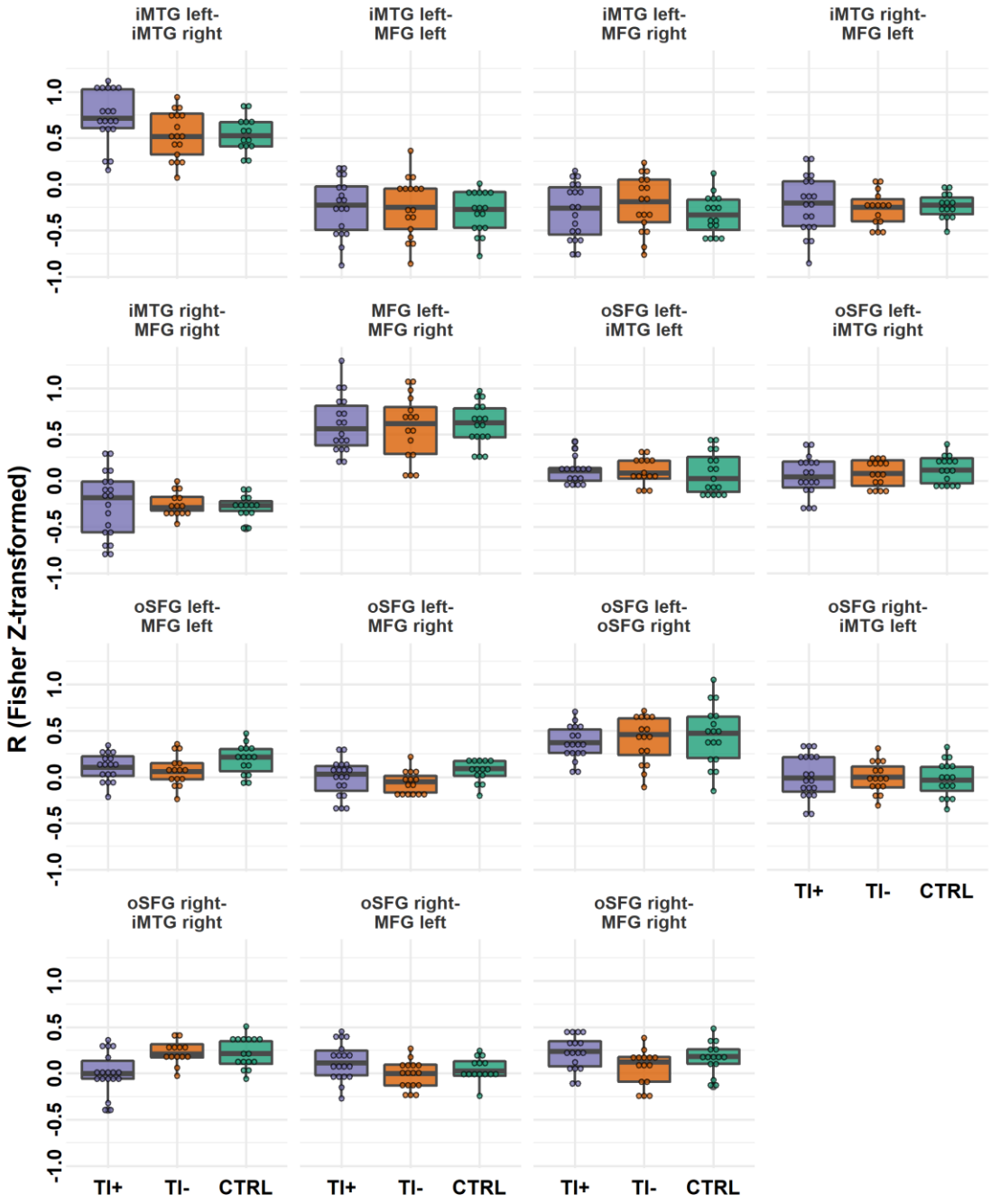

Figure S7. Functional connectivity of 15 control shifted PH-network region connections. No significant differences between the groups were observed. Control regions were derived by shifting PH-network ROIs. iMTG - inferior middle temporal gyrus, MFG - middle frontal gyrus, oSFG - orbital superior frontal gyrus. Dots represent individual values of each participant.

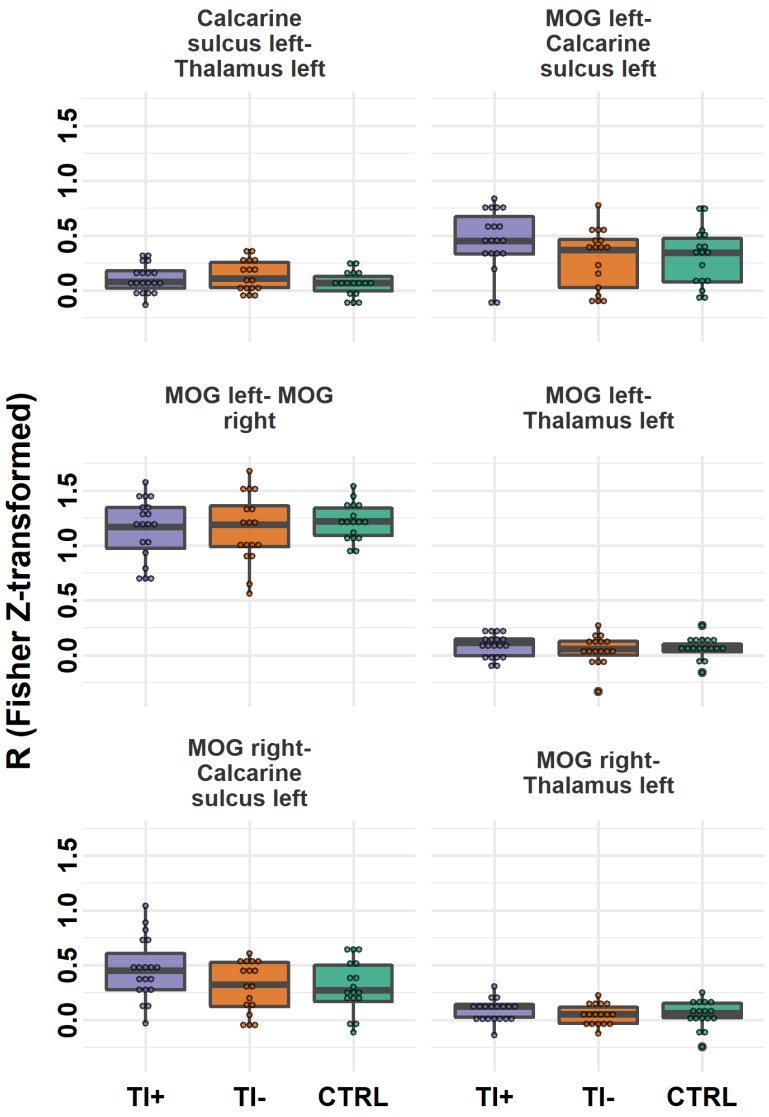

Figure S8. Functional connectivity of 6 visual network connections. No significant differences between the groups were observed. MOG – middle occipital gyrus. Dots represent individual values of each participant.

Supplementary tables

Numerosity performance	Mean ± SD	CI(95%)	t	p_{FDR}
Active, CTRL	-0.03 ± 0.08	[-0.07, 0.007]	**-4.04**	**<0.0001**
Passive, CTRL	-0.0005 ± 0.07	[-0.03, 0.03]	0.36	0.72
Active, TI-	-0.03 ± 0.04	[-0.07, 0.006]	**-4.23**	**<0.0001**
Passive, TI-	0.001 ± 0.08	[-0.03, 0.04]	0.08	0.93
Active, TI+	-0.04 ± 0.05	[-0.06, -0.01]	**-6.50**	**<0.0001**
Passive, TI+	0.008 ± 0.06	[-0.02, 0.03]	1.8	0.075

Table S1. Descriptive statistics of numerosity performance. Data are presented in mean ± standard deviation for each group (TI+ - psychotic patients with thought insertion, TI- - psychotic patients without thought insertion, CTRL – healthy controls) and condition (active, passive). CI(95%) -numerosity performance 2.5% and 97.5% confidence interval values. One sample t-test estimates and significance values corrected for multiple comparisons using FDR correction at 0.05 threshold are presented.

Comparison	t	p_{unc}	p_{FDR}
Active, CTRL - Passive, CTRL	**-4.494**	**<.0001**	**0.0001**
Active, CTRL - Active, TI-	0.372	0.711	0.999
Active, CTRL - Passive, TI-	-1.374	0.175	0.742
Active, CTRL - Active, TI+	0.409	0.684	0.99
Active, CTRL - Passive, TI+	-1.825	0.073	0.4588
Passive, CTRL - Active, TI-	1.756	0.0845	0.5016
Passive, CTRL - Passive, TI-	0.015	0.987	1.0000
Passive, CTRL - Active, TI+	1.617	0.111	0.5911
Passive, CTRL - Passive, TI+	-0.613	0.5428	0.989
Active, TI- - Passive, TI-	**-5.499**	**<.0001**	**<.0001**
Active, TI- - Active, TI+	0.095	0.924	1.0000
Active, TI- - Passive, TI+	-2.457	0.017	0.1551
Passive, TI- - Active, TI+	1.836	0.0717	0.4519
Passive, TI- - Passive, TI+	-0.719	0.0717	0.9788
Active, TI+ - Passive, TI+	**-7.620**	**<.0001**	**<.0001**

Table S2. Post-hoc analyses of numerosity performance. Between group (TI+ - psychotic patients with

thought insertion, TI- - psychotic patients without thought insertion, CTRL – healthy controls) and condition (active, passive) comparisons performing t-test and correcting for multiple comparisons using FDR correction at 0.05 threshold.

Correlation	rho	p
Active, CTRL	0.007	0.89
Passive, CTRL	0.168	0.50
Active, TI-	0.391	0.13
Passive, TI-	0.283	0.29
Active, TI+	**-0.825**	**0.002**
Passive, TI+	0.063	0.85

Table S3. Correlations between numerosity performance and executive function composite score. Spearman correlations between mean numerosity performance during the active and passive conditions and executive function composite score for each group (TI+ - psychotic patients with thought insertion, TI- - psychotic patients without thought insertion, CTRL – healthy controls

	TI+ vs TI-			TI+ vs CTRL		
Connection	**t**	**p_{unc}**	**p_{FDR}**	**t**	**p_{unc}**	**p_{FDR}**
IPL left-SMA left	-1.01	0.312	0.468	-0.60	0.551	0.678
IPS right-IPL left	**2.87**	**0.005**	**0.028**	0.42	0.678	0.678
IPS right-SMA left	-0.51	0.608	0.729	0.78	0.439	0.678
IPS right-STG left	1.16	0.247	0.468	1.56	0.120	0.361
STG left-IPL left	-0.34	0.735	0.735	0.57	0.572	0.678
STG left-SMA left	-1.17	0.242	0.468	-2.36	0.019	0.116

Table S4. Post-hoc analyses of numerosity network functional connectivity, between group comparisons. Psychotic patients with thought insertion (TI+) versus psychotic patients without thought insertion (TI-) and healthy controls (CTRL) numerosity network (6 connections) functional connectivity post-hoc comparisons. T-tests were corrected for multiple comparisons using FDR correction at 0.05 threshold. IPS – intraparietal sulcus, IPL- inferior parietal lobule, SMA – supplementary motor area, STG – superior temporal gyrus.

Correlation	IPS right - IPL left	
	r	p
Active, CTRL	0.163	0.531
Passive, CTRL	-0.071	0.787
Active, TI-	-0.168	0.519
Passive, TI-	-0.301	0.241
Active, TI+	-0.178	0.466
Passive, TI+	-0.023	0.927

Table S5. Correlations between numerosity performance and numerosity network functional connectivity affected connection in TI+ group. Pearson correlations between mean numerosity performance during the active and passive conditions and functional connectivity of numerosity network affected connection for each group (TI+ - psychotic patients with thought insertion, TI- - psychotic patients without thought insertion, CTRL – healthy controls). IPS – intraparietal sulcus, IPL- inferior parietal lobule, SMA – supplementary motor area, STG – superior temporal gyrus.

TI+ vs TI-	TI+ vs TI-			TI+ vs CTRL		
Connection	t	p_{unc}	p_{FDR}	t	p_{unc}	p_{FDR}
IFG left-IFG right	-1.37	0.171	0.367	-0.09	0.926	0.926
IFG left-pMTG left	-0.43	0.665	0.768	-0.60	0.551	0.752
IFG left-pMTG right	**-3.04**	**0.003**	**0.019**	-0.13	0.900	0.926
IFG left-vPMC left	**3.40**	**0.001**	**0.011**	**4.07**	**0.000**	**0.001**
IFG left-vPMC right	0.60	0.552	0.753	2.03	0.043	0.108
IFG right-pMTG left	-0.50	0.619	0.768	-1.68	0.094	0.201
IFG right-pMTG right	-1.78	0.075	0.250	-1.33	0.183	0.344
IFG right-vPMC left	1.74	0.083	0.250	**2.93**	**0.004**	**0.014**
IFG right-vPMC right	0.87	0.383	0.575	*2.28*	*0.023*	*0.070*
pMTG left-pMTG right	**-2.92**	**0.004**	**0.019**	**-3.63**	**0.000**	**0.002**
pMTG left-vPMC left	1.18	0.239	0.448	**2.91**	**0.004**	**0.014**

pMTG left-vPMC right	-0.27	0.785	0.841	1.08	0.280	0.461
pMTG right-vPMC left	1.44	0.150	0.367	0.51	0.607	0.759
pMTG right-vPMC right	-0.95	0.341	0.568	-1.02	0.307	0.461
vPMC left-vPMC right	0.09	0.927	0.927	0.29	0.776	0.895

Table S6. Post-hoc analyses of PH-network functional connectivity, between group comparisons. Psychotic patients with thought insertion (TI+) versus psychotic patients without thought insertion (TI-) and healthy controls (CTRL) PH-network (15 connections) functional connectivity post-hoc comparisons. T-tests were corrected for multiple comparisons using FDR correction at 0.05 threshold. IFG - inferior frontal gyrus, pMTG - posterior middle temporal gyrus, vPMC - ventral premotor cortex

Correlation	IFG left - pMTG right		pMTG left - pMTG right		IFG left - vPMC left	
	r	p	r	p	r	p
Active, CTRL	-0.186	0.542	**0.596**	**0.015**	-0.456	0.088
Passive, CTRL	-0.102	0.739	**0.603**	**0.013**	-0.301	0.276
Active, TI-	-0.321	0.209	0.191	0.533	0.167	0.568
Passive, TI-	-0.174	0.503	0.277	0.360	-0.085	0.772
Active, TI+	0.174	0.477	0.157	0.533	**0.598**	**0.009**
Passive, TI+	0.373	0.116	-0.024	0.924	0.109	0.668

Table S7. Correlations between numerosity performance and PH-network functional connectivity affected connections in TI+ group. Pearson correlations between mean numerosity performance during the active and passive conditions and functional connectivity of PH-network three connections for each group (TI+ - psychotic patients with thought insertion, TI- - psychotic patients without thought insertion, CTRL – healthy controls). IFG - inferior frontal gyrus, pMTG - posterior middle temporal gyrus, vPMC - ventral premotor cortex.

GENERAL DISCUSSION

During my thesis work, I have investigated different aspects related to self-monitoring, which is important for a coherent self-representation and orientation in the surroundings. With my research, I contributed to a better understanding and provided new insights into mechanisms related to self-monitoring, which alterations could account for the manifestation of psychotic symptoms such as passivity experiences.

4.1 SUMMARY OF SCIENTIFIC CONTRIBUTIONS AND OUTLOOK

Part I of the thesis combined two articles investigating functional connectivity alterations within the specific network related to alienation (PH-network) in psychotic patients with passivity experiences and individuals at high risk for psychosis development. In Part II of the thesis, which comprises two studies, I have studied a different aspect related to self-monitoring: self-generated signal attenuation during a higher-level cognitive function of numerosity estimations in healthy volunteers and whether it is affected in psychotic patients with thought insertion.

4.1.1 PH-network to study alienation mechanisms in psychotic patients

Passivity experiences such as thought insertion, auditory verbal hallucinations and somatic passivity are frequent symptoms of psychosis. During passivity experiences, self-generated actions, thoughts or emotions are perceived as not self-generated but caused by an external entity (e.g., alienation). To investigate the alienation aspect of passivity experiences, we used a recently described PH-network (see Annexes: Bernasconi et al., 2020). In Study 1, we explored whether we could distinguish psychotic patients with versus without passivity experiences based on the PH-network functional connectivity. As hypothesized, we have observed functional connectivity reduction in psychotic patients with passivity experiences. This reduction was between the right pMTG and bilateral IFG within the PH-network. Noteworthy, we have found similar alterations specific to psychotic patients with thought insertion as compared to the patients without thought insertion (Study 4). In this cohort of patients, we have observed functional connectivity reduction between the right pMTG and

the left IFG and the bilateral pMTG. Additionally, we observed increased functional connectivity in psychotic patients with thought insertion between the left IFG and the left vPMC. Considering these findings, we suggest that functional connectivity reduction between fronto-temporal areas within the PH-network could be a specific alteration linked to alienation across various passivity experiences. In contrast, the increase of connectivity observed in psychotic patients with thought insertion between the left frontal areas could be related to a symptom-specific alteration. Similar functional connectivity reduction has been found as well in Study 2 while investigating individuals with 22q11 deletion syndrome who are at high risk of developing psychosis. There we have found reduced functional connectivity between the right pMTG and the left IFG and the bilateral pMTG, and additionally the right pMTG and the left vPMC when compared against age-matched controls. These findings provide a possibility to use PH-network functional connectivity for predictions of the psychosis development and better understanding of mechanisms related to specific psychotic symptoms.

Fronto-temporal disconnection

Following on the main finding that all the aforementioned clinical populations (psychotic patients with passivity experiences, thought insertion and 22q11; Figure 4.1) had functional disconnection within the fronto-temporal areas of the PH-network, we propose that this alteration could be a significant neural underpinning, leading to alienation (experiencing an alien entity causing the sensations or actions) in psychotic passivity experiences. It is important to mention that similar fronto-temporal disconnection has been observed in neurological patients with symptomatic PH such as Parkinson's disease (see Annexes: Bernasconi et al., 2020) and dementia with Lewy bodies (see Annexes 5.5.1 section). The findings that patients with symptomatic PH have similar alterations strengthens the importance of the PH-network as a neural mechanism to study the alienation aspect in psychotic patients. Fronto-temporal functional connectivity reductions stand in line with the disconnection hypothesis for hallucinations, observed in many clinical studies in schizophrenia patients (Crossley et al., 2009; Karbasforoushan and Woodward, 2013; Oertel-Knöchel et al., 2014). These have been linked to altered prediction mechanisms, suggesting that delayed prediction signal due to disconnectivity causes self-other misattribution (Frith et al., 2000; Lawrie et al., 2002; Friston et al., 2016). We show that a symptom-specific network (PH-network) complements the findings of functional disconnection observed during whole-

brain analysis (Crossley et al., 2009; Karbasforoushan and Woodward, 2013; Oertel-Knöchel et al., 2014). This offers an advantage, compared to whole-brain analysis for understanding the neural mechanisms related to alterations for a specific symptom aspect such as alienation. For PH, this is particularly relevant, given it has been linked to the sensorimotor self-monitoring deficits (Bernasconi et al., 2020; Blanke et al., 2014; Salomon et al., 2020) and related to the global bodily self-consciousness (Blanke, 2012; Blanke et al., 2015, 2014), enabling us to speculate the causality of the alienation aspect. Thus, we propose that alienation is related to the fronto-temporal disconnection affecting the correct self-monitoring during sensorimotor global bodily perceptions.

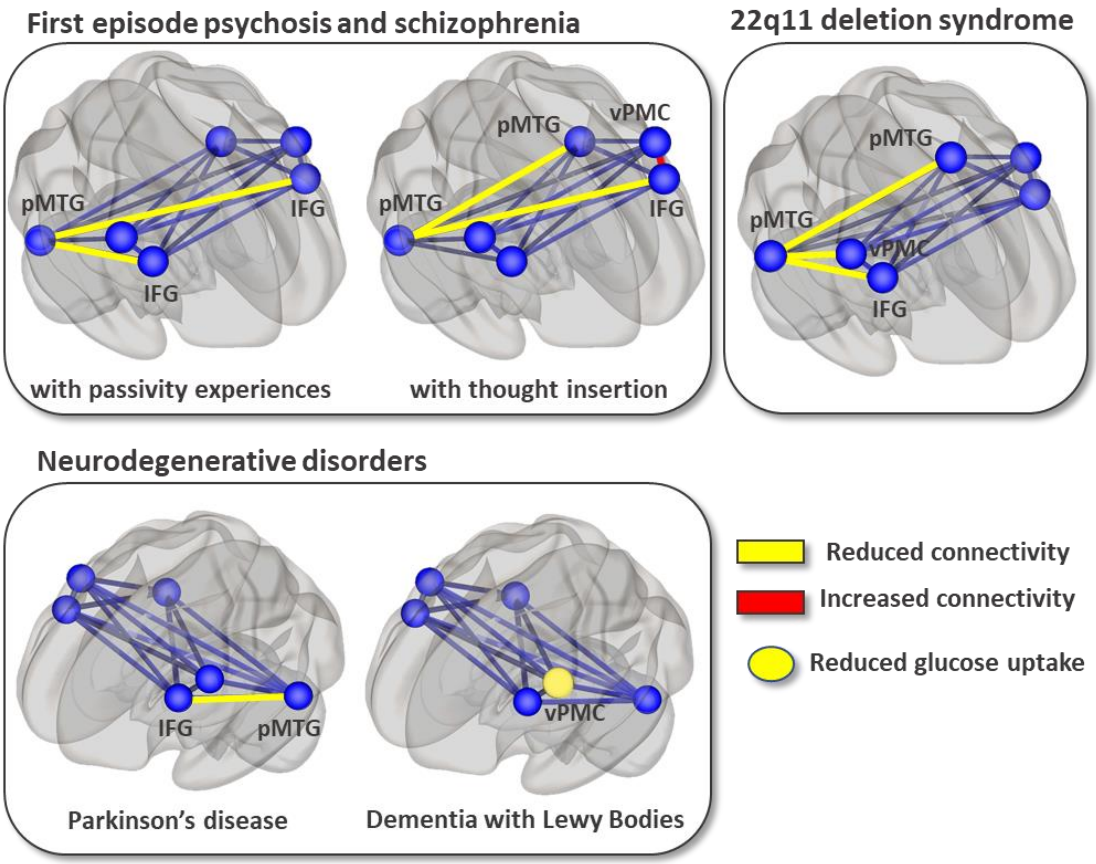

Figure 4.1. Overview of the PH-network (depicted in blue) alterations across the investigated clinical populations. Fronto-temporal reduced functional connectivity (depicted in yellow) was observed in most of the tested clinical populations. Additionally, patients with thought insertion (top middle) had increased functional connectivity between the left IFG and left vPMC (depicted in red). The study in Dementia with Lewy Body patients (bottom right) investigated PET imaging data by looking at the mean glucose uptake within the PH-network; reduced glucose uptake was observed in the left vPMC (depicted in yellow). pMTG – posterior middle temporal gyrus, IFG – inferior frontal gyrus, vPMC – ventral premotor cortex.

Dynamic functional connectivity

Further developments regarding the PH-network analysis method could be introduced. Currently, the studies were performed analyzing static functional connectivity, meaning that the correlations between ROIs were averaged over the whole period of data acquisition. This method is excellent for observing significant and prominent differences between the groups. Yet, knowing that the brain activity is fluctuating over time even at rest, it would be interesting to see how it varies within the PH-network across different clinical populations. Recent developments in the fMRI field offer more advanced methods, such as co-activation pattern analysis (CAPs) (Liu et al., 2018). CAPs allow investigating connectivity fluctuations over time by defining different states/ patterns. The principle of this method is to look for brain regions co-activating with the seed ROI in moments of significant BOLD activity of the seed ROI. The performed studies in this thesis showed that the PH-network areas of the pMTG and the IFG are of the most importance as the alterations between these regions have been observed consistently. Using these regions as seeds in CAPs analysis over different clinical populations has the potential to provide further insights about the brain networks underlying PH and passivity experiences and refine the observed network alterations in improved spatio-temporal features.

Future studies in clinical populations

The studies included in this thesis were the first attempt to investigate the relevance of the PH-network as a potential mechanism to explain alienation in psychotic patients. Further developments in researching PH link to psychotic symptoms such as passivity experiences should be conducted. In the next section, I will discuss some possible studies that could be designed to develop the field.

Future studies should directly evaluate the occurrence of PH among psychotic patients with passivity experiences (PE). For example, designing the study with four patient groups: PH+PE+, PH+PE-, PH-PE+, and PH-PE- would give a more comprehensive insight on how PH neural mechanisms link to passivity experiences. Further, based on the present data, future studies should evaluate patients' sensitivity to robot-induced PH (Bernasconi et al., 2020; Blanke et al., 2014) and how this affects auditory-verbal processing (Orepic et al., 2020; Salomon et al., 2020) or thought monitoring (see Annexes: Serino et al., *in revision*) and other mechanisms

related to different passivity experiences, allowing for more detailed evaluations of how passivity experiences and PH and their respective brain networks are linked in psychosis. It would be interesting to dissect the specific alterations within the PH-network and other brain areas related to the symptom separately (e.g., auditory verbal hallucinations, somatic passivity, etc.) and common features of all passivity experiences.

Regarding the PH-network functional connectivity as a biomarker for the development of psychosis, longitudinal studies investigating individuals with 22q11 deletion syndrome should be conducted. Tested individuals with 22q11 deletion syndrome were still asymptomatic (no psychotic symptoms), but significant differences were already observed within the PH-network functional connectivity compared to the age-matched healthy controls (Study 2). A follow-up study, including individuals with and without psychotic symptoms and assessing the occurrence of PH over several time points, would allow an extensive understanding of the development of psychotic symptoms and relation to PH. The current ongoing studies investigating individuals with 22q11 deletion syndrome are now including the assessment of PH with a newly developed questionnaire by our laboratory. Preliminary data, including 76 patients of the longitudinal cohort, shows that around 20% of the individuals with 22q11 deletion syndrome experience PH. More data should be collected over several time points and combined with the imaging data to explore the developmental impact of PH on the manifestation of psychotic symptoms.

4.1.2 Cognitive self-attenuation

An important aspect of self-monitoring is the attenuation of self-generated signals. This attenuation has been previously described in visual, auditory and somatosensory domains (e.g., Benazet et al., 2016; Kilteni and Ehrsson, 2019; Whitford, 2019). It has been extended to cognitive processes related to sensory modalities such as motor imagery or inner speech (e.g., Kilteni et al., 2018; Whitford et al., 2017). Yet, up to date, it was not investigated whether the attenuation of self-generated signals applies to higher-level cognitive processes beyond the sensorimotor system. In this thesis (Part II), we have investigated self-attenuation during the higher-level cognitive function by comparing numerosity estimations for self- (active condition) and externally (passive condition) generated words. We hypothesized to observe a bigger underestimation of self-generated words compared to externally generated words. For the first time, we have developed a well-controlled paradigm adapted to the fMRI

environment, allowing such comparisons (Study 3). As hypothesized, we have found attenuated (expressed in bigger underestimation) numerosity estimations for self-generated words compared to externally-generated words. The underestimation in general was found to be associated with the right IPS – a key area for numerosity processing (Arsalidou and Taylor, 2011). Crucially, increased connectivity was observed during the active condition between the right IPS and extended network including SMA, STG and IPL. We propose that the network associated with the right IPS could provide neural underpinnings of attenuation processing. Both, SMA, an important brain area for voluntary action planning (Deiber et al., 1999; Lau et al., 2004; Timm et al., 2014) and parietal cortex including IPL, associated with perceptual and predicted information integration (Rizzolatti et al., 2008), have been shown to be involved in attenuation processes over different domains (Bansal et al., 2018; Brooks and Cullen, 2019; Haggard and Whitford, 2004; Jo et al., 2019).

In addition, in this study, we were also interested in exploring whether attenuation can even be observed for consecutive cognitive processing, such as error estimation about the performed numerosity judgments (performance monitoring). We did not find a behavioral difference for performance monitoring between the active and passive conditions, suggesting that attenuation does not concern performance monitoring at the behavioral level. However, examining the imaging data, we observed signal attenuation during the active compared to the passive condition in the bilateral insula and putamen. The findings at the neural level imply that the attenuation of the signal is reflected during error estimations. Yet, it is possible to speculate that more complex processing for the performance monitoring during the active and passive conditions which enables similar behavioral output, is at play. Thus, such process could involve different cognitive systems like decision making (Balleine et al., 2007; Kim and Im, 2019) as distinct modulation of striatal parts (caudate nucleus and putamen) between conditions was observed.

In study 4, we investigated the cognitive self-attenuation using a similar paradigm in psychotic patients with and without thought insertion and healthy controls. The study aimed to unravel whether cognitive self-attenuation is altered in psychotic patients with thought insertion and could be associated with the loss of subjective experience like a sense of thought agency. This study was carried out by performing the numerosity estimation task outside the fMRI scanner, which allowed participants to generated words out loud. As it was observed in the previous

study (Study 3), in this study, all three groups had bigger underestimation (attenuation) during the active compared to the passive condition. Despite the hypothesis of reduced self-attenuation in psychotic patients (Bansal et al., 2018; Ford et al., 2014; Pynn and DeSouza, 2013; Shergill et al., 2014, 2005), we did not observe significant differences between the groups, suggesting that there could be a more complex relationship between cognitive self-attenuation and other processes related to the thought insertion phenomenon.

Given that the participants in this study were primarily recruited for a larger study cohort, the access to rs-fMRI data and neuropsychological assessments was available. This allowed for a more in-depth investigation of the relationship between the cognitive self-attenuation and the affected executive functioning, as this is one of the main traits of psychotic patients (Mesholam-Gately et al., 2009). Indeed, a significant negative correlation between cognitive self-attenuation levels and executive function composite score was observed only in psychotic patients with thought insertion. In other words, the less self-attenuation (lower underestimation) during the active condition, the lower executive functioning was found. No significant relationship was observed for control groups or passive condition. It is possible to conclude that cognitive self-attenuation is closely related to the executive dysfunction in psychotic patients with thought insertion and this observed relationship could partly explain the discrepancies contributing to the occurrence of thought insertion.

We have also thus investigated functional connectivity within the network associated with the attenuation processing during numerosity estimations (as was found in Study 3) in the rs-fMRI data of psychotic patients with thought insertion. We have observed increased functional connectivity in psychotic patients with compared to without thought insertion between the right IPS and the left IPL, suggesting insufficient attenuation at the neural level related to the cognitive processes like numerosity estimations.

Dynamic causal modeling

The further improvement of the currently performed analyses in Study 3 could be applied to investigate the causality of the observed connectivity modulation during the active compared to the passive conditions in the network of the right IPS, bilateral SMA, left IPL and left STG. I proposed (see above) that the observed functional connectivity between these areas could provide a neural signature for the behavioral self-attenuation. However, the current analysis

cannot conclude the causality of this relationship. I hence consider that additional analysis, such as dynamic causal modeling (Friston et al., 2019, 2003) that investigates effective connectivity between the distinct brain regions and conditions would be of great relevance.

Future clinical studies

To understand in more depth the mechanisms related to cognitive self-attenuation in psychotic patients with thought insertion, it would be relevant to conduct the fMRI study while performing a numerosity estimation task (as in Study 3). It would help to reveal directly what brain mechanisms are engaged and possibly altered as compared to healthy controls and psychotic patients without thought insertion. Additionally, the studies should also include robotic manipulation, which can induce PH while acquiring fMRI data (see Annexes: Bernasconi et al. 2020, for the fMRI study inducing PH). This would allow not only to understand the mechanisms of cognitive-self attenuation better but also would provide a possibility to study the direct influence of PH for cognitive self-monitoring.

4.2 TWO DISTINCT MECHANISMS RELATED TO SELF-MONITORING ARE ACCOUNTING FOR THE PSYCHOTIC PASSIVITY EXPERIENCES

The presented research in this thesis culminates with Study 4, where we have investigated the possible mechanisms accounting for one of the passivity experiences - thought insertion. In this study, the aim was to examine different aspects of thought insertion phenomenon: a negative aspect defined as loss of the subjective experience such as a sense of agency or ownership (e.g., thoughts are perceived as not self-generated) and a positive aspect accounting for experiencing an alien entity (e.g., someone else put the thoughts in one's mind). Mechanisms accounting for the self-attenuation are important for the sense of agency (Haggard, 2017), allowing us to study the negative aspect of TI. Importantly, it was shown in several studies that self-attenuation is reduced in schizophrenic patients (Bansal et al., 2018; Ford et al., 2014; Pynn and DeSouza, 2013; Shergill et al., 2014, 2005). Here, we employed a numerosity estimation task (based on Study 3 and study by Serino et al., *in revision,* see Annexes) to investigate whether cognitive self-attenuation is affected in psychotic patients with thought insertion. We hypothesized that the phenomenon of thought insertion involves internal cognitive processes where sensorimotor systems are not involved (e.g., auditory

cortex alterations have been shown in psychotic patients with auditory verbal hallucinations; Whitford, 2019). As mentioned in the above section, we had observed a relationship between affected executive functioning and varying levels of cognitive self-attenuation in psychotic patients with thought insertion, suggesting that higher-level cognitive processes are associated with thought insertion.

We investigated neural mechanisms related to the positive alienation aspect of thought insertion in the PH-network. We have found reduced connectivity between fronto-temporal, temporal areas within the PH-network, standing in line with the disconnection hypothesis for hallucinations (Friston, 1998; Hahamy et al., 2014; Karbasforoushan and Woodward, 2013; Skudlarski et al., 2010). Interestingly, altered increased connectivity between the left IFG and left vPMC was found in psychotic patients with thought insertion. This increased connectivity significantly correlated with varying levels of cognitive self-attenuation. In other words, the higher the functional connectivity was observed, the lower self-attenuation was in psychotic patients with thought insertion. These findings suggest a link between two possible mechanisms accounting for thought insertion.

The observed association stands in line with the previous study in healthy volunteers (see Annexes: Serino et al., *in revision*), where the numerosity estimation task (same as in Study 4) was performed while manipulating a robotic device which induces mild sensations of PH (as in Study 2). It was found that participants' cognitive self-attenuation was reduced while operating the robotic system in asynchronous mode (with spatio-temporal delay, condition inducing PH) compared to synchronous mode (control condition). Importantly, the stronger a participant experienced the PH, the more self-attenuation during numerosity estimations was reduced in the asynchronous (compared to the synchronous) condition. The study provides direct evidence that sensorimotor alterations inducing PH affected the self-monitoring on the cognitive level. Further, by assessing questionnaires about the subjective feelings while performing this task, participants reported the elevated sensations of thought alienation, mimicking the aspects which are weaker in intensity as experienced by psychotic patients with thought insertion.

Altogether, the discussed studies implied that the mechanisms accounting for the positive and negative aspects of the symptom are related (shown in Study 4 and Serino et al., *in*

revision). The neural mechanisms accounting for the experience of an alienation (e.g., PH-network) should be functionally related to the areas involved in thinking processes. Alterations in the mechanisms of one of the aspects (negative or positive) would not be enough for the passivity experience to occur. For example, it has been shown that in the case of unbidden thoughts, the sense of thought agency is disrupted, but the experience that someone else puts the thoughts into one's mind (alienation) is not occurring (Gallagher, 2004; Martin and Pacherie, 2013).

We propose that both aspects (negative and positive) should be altered and related in order to the passivity experiences to occur. Experiencing an alien entity during the passivity experiences is described by a definition of the symptoms (Kendler and Mishara, 2019; Schneider, 1957). This suggests that PH could be co-experienced simultaneously as other passivity experiences. However, there is no study showing this relationship. We speculate that depending on the level of the affected systems (e.g., functional connectivity alterations in brain areas related to different domains, like auditory or somatosensory), it is possible to experience one type of passivity experience or several of them. For example, if the alterations in the PH-network are substantial, the PH would occur, and if the relationship between the PH-network and other brain areas is affected, it would give rise to distinct passivity experiences. Hence, future studies should be conducted to understand the mechanistic links between PH and passivity experiences better.

Previously discussed behavioral and neuroimaging findings suggest that mechanisms of PH are related to thought insertion and other passivity experiences and could account for the alienation aspect of the symptom. Importantly, PH-network functional connectivity alterations were linked to self-monitoring during higher-level cognitive processes such as numerosity estimations (Study 4). More precisely, cognitive self-attenuation in psychotic patients with thought insertion was negatively related to the altered functional connectivity with the frontal connection of the PH-network. Moreover, healthy volunteers who were exposed to the PH inducing stimulation while performing a numerosity estimation task had affected thought monitoring (see Annexes: Serino et al., *in revision*). Thus, neural and behavioral mechanisms accounting for the PH (Blanke et al., 2014; Bernasconi et al., 2020) could account for the positive aspect (alienation) of passivity experiences (Study 1 and 4). Altered self-monitoring related to the loss of subjective experience such as self-agency or

ownership as was shown in previous studies (Bansal et al., 2018; Ford et al., 2014; Pynn and DeSouza, 2013; Shergill et al., 2014, 2005) and Study 4 could account for the negative aspect. Both of these aspects are related to the self-monitoring but are processed differently. PH is linked to global bodily self-monitoring deficits (Blanke et al., 2014; Bernasconi et al., 2020), while the loss of sense of agency over actions, thoughts or emotions are more related to the affected domain (Bansal et al., 2018; Ford et al., 2014; Pynn and DeSouza, 2013; Shergill et al., 2014, 2005).

4.3 CONCLUSIONS

To conclude, this work adds to a more comprehensive understanding of the neural and behavioral self-monitoring related mechanisms involved in the manifestation of psychotic symptoms over different clinical populations. We show that psychotic symptoms, specifically passivity experiences, are associated with reduced fronto-temporal functional connectivity within the network accounting for an alien entity (PH-network). For the first time, we showed that self-attenuation applies to the higher-level cognitive function of numerosity estimations, extending previous accounts of self-attenuation regarding sensory processing. It offers a promising tool to study clinical cases in which such attenuation may be altered, including patients with passivity experiences such as thought insertion. Together, these findings open the doors to investigate specific relationships between the PH, cognitive self-attenuation and passivity experiences, which could lead to better diagnosis and prognosis of psychosis development.

ANNEXES

During my thesis, I have been involved in several other projects that are briefly described here and part of them are added as additional papers.

5.1 ONGOING STUDIES

5.1.1 PH-network investigation in Dementia with Lewy Bodies patients

I am currently finalizing the clinical imaging study, where I have investigated metabolic changes (glucose uptake, PET imaging) within the PH-network in Dementia with Lewy Bodies (DLB) with and without symptomatic PH. I have found reduced glucose uptake in the left vPMC of the PH-network in DLB patients with PH compared to without. This finding stands in line with the disconnection hypothesis for hallucinations and corroborates previous observations of reduced metabolic activity in DLB patients. We also have observed that vPMC has distinct correlations maps with the whole brain in patients with and without PH. Specifically, DLB patients with PH show very minimal correlations between left vPMC and the rest of the brain including only the bilateral caudate nucleus and midbrain. Contrary, DLB patients without PH show widespread cortical correlations with the left vPMC. Furthermore, a significant negative correlation has been observed between glucose uptake levels in the left vPMC and presynaptic dopamine levels in the left caudate nucleus in DLB patients with PH.

5.1.2 A pharmacological longitudinal study in 22q11 deletion syndrome

In collaboration with the laboratory of Developmental Imaging and Psychopathology directed by Professor Stephan Eliez (NCCR-Synapsy project), the ongoing longitudinal study investigating the dopaminergic system in individuals with 22q11 deletion syndrome is investigated. The specific project where our lab is contributing aims at a more comprehensive understanding of the dopaminergic treatment role in multisensory integration and the induction of psychosis-like states such as PH and PE. The experimental setup is the same as described in the annexed study conducted by Bernasconi, Blondiaux and colleagues, 2020 (see in Annexes section). The participants are tested at different time points: before, during, and after the treatment. I was involved in the data collection for this project which is still ongoing.

5.2 SENSORIMOTOR HALLUCINATIONS IN PARKINSON'S DISEASE

One Sentence Summary

Presence hallucination in Parkinson's disease (PD) is shown to arise from errors in sensorimotor integration and fronto-temporal disconnection, potentially indicating a more severe form of PD that has been associated with psychosis and cognitive decline.

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Authors' contributions

FB designed Study 1 and 3, collected & analyzed data, conducted clinical interviews, wrote paper; EB designed Study 2, collected & analyzed data, wrote paper; J. Potheegadoo collected data, designed questionnaire for semi-structured interview, conducted clinical interviews and clinical evaluations for study 1; **GS analyzed data for study 3**; J. Pagonabarraga, HB and JK recruited patients, conducted clinical interviews, collected data for study 3; MA and NF analyzed data for study 2; MB collected data, conducted clinical interviews and clinical evaluations for study 1; MF collected data for study 1; SK coordinated the recruitment for

study 1; SMH designed and conducted clinical interviews for study 3; FS collected data for study 3; MH designed and developed the robotic systems; JH, JG, PB recruited patients and conducted clinical evaluations for study 1; DV designed study 2; PK designed study 1; GR and OB designed study 1, 2 and 3, wrote paper. All authors provided critical revisions and approved the final version of the paper for submission. All authors declare no competing interests.

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Summary

Hallucinations in Parkinson's disease (PD) are disturbing and frequent non-motor symptoms and constitute a major risk factor for psychosis and dementia. We report a robotics-based approach applying conflicting sensorimotor stimulation, enabling the induction of a clinically-relevant hallucination called presence hallucination (PH), and the characterization of a PD subgroup with enhanced sensitivity for conflicting sensorimotor stimulation and robot-induced PH. We next identify the fronto-temporal network of PH by combining MR-compatible robotics (and sensorimotor stimulation in healthy participants) and lesion network mapping (neurological non-PD patients). This PH-network was selectively disrupted in a new and independent sample of PD patients, predicted the presence of symptomatic PH, and associated with cognitive decline. These robotics-neuroimaging findings extend existing sensorimotor hallucination models to PD and reveal the pathological cortical sensorimotor processes of specific hallucinations (PH) in PD, potentially indicating a more severe form of PD that has been associated with psychosis and cognitive decline.

Introduction

The vivid sensation that somebody is nearby when no one is actually present and can neither be seen nor heard (i.e. sense of presence or presence hallucination, PH), has been reported from time immemorial and found its way into the language and folklore of virtually all cultures (1–3). Following anecdotal reports of PH by extreme mountaineers (4), solo-sailors and shipwreck survivors (5), PH have also been described in a variety of medical conditions including schizophrenia (1, 6), epilepsy, stroke, brain tumors (7–9) and Parkinson's disease (PD) (10–12).

Whereas PH are very rare manifestations in most medical conditions, they are more frequent in PD and may occur as a recurrent neuropsychiatric complication, affecting many PD patients with PH on a weekly and some on a daily basis (10). Thus, PH occur in approximately 50% of patients with PD (10–13) and are generally grouped with so-called minor hallucinations, which include, next to PH, passage hallucinations (i.e. rapid perception of a person or animal passing sideways in the periphery of the visual field) and visual illusions (i.e. visual misperceptions of objects) (11). Minor hallucinations are the most prevalent and earliest type of hallucination in PD (11, 12), often preceding the onset of structured visual hallucinations (17), and may even be experienced, by one-third of patients, before the onset of first motor symptoms (18).

Hallucinations in PD increase in frequency and severity with disease progression and are one of the most disturbing non-motor symptoms (11, 12, 14). Importantly, hallucinations in PD are associated with major negative clinical outcomes such as chronic psychosis, cognitive decline and dementia, as well as higher mortality (10, 11, 15–17). While these associations have mostly been observed for PD patients with structured visual hallucinations, growing clinical evidence suggests that they may also be valid for PH. This is clinically relevant also because PH often appear before structured visual hallucinations (11). Yet, despite their high prevalence and association with major negative clinical outcome, PH (and other hallucinations) remain underdiagnosed (11, 12, 18, 19), caused by patients' reluctance to report hallucinations and clinicians' failure to ask about them (20, 21).

Several important studies have investigated visual and cognitive brain mechanisms in PD patients with hallucinations, revealing distributed structural changes in visual cortex (in lateral

and ventral occipito-temporal areas, in fusiform gyrus, and in visual parietal areas), but also retinal changes (for a review see 22). Moreover, several visual deficits have been observed in PD including contrast sensitivity (23, 24), visuo-spatial attention (25), color vision (24), and biological motion perception (26) and described as possible alterations leading to hallucination (22). We note, however, that these studies mostly focused on patients with structured visual hallucinations (22) or did not evaluate minor hallucinations, including PH. Comparable studies are rare or lacking for PH (or other minor hallucinations) and, accordingly very little is known about the location and distribution of early brain changes and behavioral consequences in PD patients with PH and how they may associate with more severe and disabling structured visual hallucinations and cognitive deficits (11, 27).

Early neurological work investigated PH following focal brain damage and classified PH among disorders of the body schema, suggesting that they are caused by abnormal self-related bodily processes (9, 28). More recent data corroborated these early findings and induced PH repeatedly by electrical stimulation of a cortical region involved in sensorimotor processing (8). By integrating these clinical observations with human neuroscience methods inducing bodily illusions (29–32), we have designed a method able to robotically induce PH (robot-induced PH or riPH) in healthy participants (33). This research demonstrated that specific sensorimotor conflicts, including bodily signals from the arm and trunk, are sufficient to induce mild to moderate PH in healthy participants, linking PH to the misperception of the source and identity of sensorimotor signals of one's own body.

Here, we adapted our robotic procedure to PD patients and elicited riPH, allowing us to characterize a subgroup of patients that is highly sensitive to the sensorimotor procedure, and to identify their aberrant sensorimotor processes (study 1). We next determined the common PH-network in frontal and temporal cortex, by combining MR-compatible robotics in healthy participants with brain network analysis in neurological non-PD patients with PH (study 2). Finally, we recorded resting-state fMRI data in a new and independent sample of PD patients and identified pathological functional connectivity patterns within the common PH-network, which were predictive for the occurrence of PD-related PH (study 3).

Results

riPH in patients with PD (study1.1)

Based on semi-structured interviews, patients with PD were grouped into those who reported symptomatic PH, sPH (PD-PH; n=13), and those without sPH (PD-nPH; n=13) (Supplementary S1-2, Tab.S1-2). Patients were asked to actuate a robotic device and were exposed to repetitive sensorimotor stimulation that has been shown to induce PH in healthy participants in a controlled way (33). In study1.1, we assessed whether robotic sensorimotor stimulation induces PH in patients with PD and whether such riPH differ between PD-PH and PD-nPH, hypothesizing that PD-PH patients are more sensitive to the robotic procedure.

In the robotic sensorimotor paradigm, participants were asked to perform repetitive movements to operate a robot placed in front of them, which was combined with a back robot providing tactile feedback to participants' backs (Fig.1A). Based on previous data (30, 33, 34), tactile feedback was delivered either synchronously with patients' movements (synchronous control condition, a spatial conflict is present between movement in front and touch on the back) or with a 500ms delay (asynchronous condition) associated with an additional spatio-temporal sensorimotor conflict shown previously to induce PH (33) (Supplementary S3).

The robotic procedure was able to induce PH in patients with PD. Importantly, PD-PH patients rated the intensity of riPH higher than PD-nPH patients (main effect of Group: permutation p-value=0.01) (Fig.1B). Confirming the general importance of conflicting asynchronous sensorimotor stimulation (30) for riPH, both sub-groups gave higher PH ratings in the asynchronous versus synchronous condition (main effect of Synchrony: permutation p-value=0.045) (Fig.1C) (Supplementary S4 for additional results). Other robot-induced bodily experiences (e.g. illusory self-touch) also confirmed previous findings (33) (Supplementary S5) and no differences were observed for the control items (all permutation p-values>0.05). These results show that PH can be safely induced by the present robotic procedure under controlled conditions in patients with PD. Such riPH were modulated by sensorimotor stimulation with asynchronous robotic stimulation resulting in higher ratings in all tested groups, and, importantly, PD-PH (vs. PD-nPH) reported stronger riPH, linking the patients' usual sPH to experimental riPH and showing that PD-PH patients were more sensitive to our robotic procedure.

Post-experiment debriefing revealed 38% of PD-PH patients who reported riPH that were comparable (or even stronger) in intensity to the patients' usual sPH in daily life. One PD-PH patient, for example, described his riPH as "an adrenaline rush. Like something or someone was behind me, although there is no possibility to have someone behind" (Video S1, for additional reports Supplementary S6). Interestingly, all such instances were reported after asynchronous stimulation. Moreover, PD-PH patients often experienced riPH on their side (and not on their back, where tactile feedback was applied), revealing a further phenomenological similarity between riPH and PD patients' usual sPH (10) and suggesting that we induced a mental state that mimics sPH (Supplementary S7-8).

Data from study1.1 reveal that riPH can be safely induced by the present procedure, are stronger in patients who report sPH (PD-PH), and that such riPH share phenomenological similarities with PD-related sPH. These findings cannot be related to a general response bias related to PD, because riPH were absent or weaker in PD-nPH and because the control items showed no effects in any of the participant groups.

riPH in PD-PH patients depend on sensorimotor delay (study1.2)

Previous work investigated the effects of systematically varied sensorimotor conflicts (i.e. delays) on somatosensory perception, enabling the induction and modulation of different somatic experiences and illusions (34–36). Sensorimotor processing and the forward model of motor control (37, 38) are prominent models of hallucinations (39, 40) and it has been proposed that deficits in predicting sensory consequences of actions causes abnormal perceptions and hallucinations (39–41). In study1.2, we assessed whether riPH depend on the degree of conflict applied during sensorimotor stimulation, by inserting variable delays between the movements of the front robot (capturing movements of the forward-extended arm) and the back robot (time of tactile feedback on the back). In each trial, participants (Supplementary S9) were exposed to a randomly chosen delay (0-500ms, steps of 100ms). After each trial, participants were prompted whether they experienced a riPH or not (yes-no response, Supplementary S10). We investigated whether the intensity of riPH increases with increasing delays in PD patients (showing that PH are modulated by increasing spatio-temporal conflicts) and whether PD-PH have a higher spatio-temporal delay sensitivity than PD-nPH.

As predicted, study1.2 shows that the intensity of riPH increased with increasing spatio-temporal conflict (main effect of delay: permutation p-value=0.014) and that this delay dependency differed between the two patient groups, showing a higher delay sensitivity in PD-PH patients (interaction Group*delay: permutation p-value=0.039) (Fig.1D) (Supplementary S11, Fig.S1). Control analysis (Supplementary S12) (Fig.1E-F, Fig.S2) allowed us to exclude that the observed differences (in riPH ratings between patient groups) are due to differences in movements of the arm and related tactile feedback during the robot actuation (Supplementary S13). In addition, these differences in riPH between PD-PH and PD-nPH cannot be explained by differences in demographic or clinical variables (including anti-parkinsonian medication, motor impairment, gender, cognitive functions; all permutation p-values>0.05) (Supplementary S14, Tab.S1). Finally, it could be argued that our procedure may have induced a mere tactile hallucination or misperception. However, this is not the case, because our procedure manipulated specific sensory and motor mechanisms, which did not only involve tactile stimulation on the back, but involved additional proprioceptive, tactile and motor cues (from the upper limb) as well as additional robotically-controlled spatio-temporal cues (related to the incongruency between these proprioceptive-tactile-motor signals). Importantly, tactile cues alone are not sufficient to induce riPH: if riPH were tactile hallucinations or misperceptions then every experimental condition (e.g. even the synchronous condition) should lead to PH, because they also contain tactile cues. However, this was neither the case in studies1.1 and 1.2 nor in previous work (33, 42) (see Supplementary S14).

Based on previous results using robotics and conflicting sensorimotor stimulation (34–36), these data from study1.2 extend those of study1.1 and reveal abnormal perceptual processes in PD-PH patients when exposed to different sensorimotor conflicts, characterized by experiencing stronger riPH and a higher sensorimotor sensitivity. These findings are compatible with an alteration of sensorimotor brain processes associated with the forward model and its role in hallucinations in PD-PH patients (39, 40, 43).

Brain mechanisms of PH

Neuroimaging work on sPH and other minor hallucinations in PD patients has described structural alterations and aberrant functional connectivity in different cortical regions (27, 44). Despite these clinical neuroimaging findings, it is not known whether the regions

associated with sPH of neurological non-parkinsonian origin (33) are also altered in PD patients with PH. Moreover, because the brain networks of riPH have never been investigated, it is also not known whether the abnormal sensorimotor mechanisms described in PD-PH patients (study1) are associated with a disruption of brain networks of riPH. To determine the brain mechanisms of PH, we first adapted an MR-compatible robot (45) (Supplementary S15) and applied sensorimotor stimulations while recording fMRI during riPH in healthy participants and identified the associated brain networks (study2.1). We then combined this network with evidence from sPH of neurological non-parkinsonian origin (study 2.2) and, finally, applied this common network to PD patients (study3).

Brain mechanisms of riPH in healthy participants using MR-compatible robotics (study2.1)

Based on behavioral pilot data (Supplementary S16-S17, Tab.S5), we exposed 25 healthy participants to asynchronous and synchronous robotic stimulation while recording fMRI (Fig.2A, Video S2, Supplemental S15, Fig.S3). Our behavioral data replicated previous results ((33), study1 and pilot study) and we found that asynchronous vs. synchronous robotic stimulation induces stronger PH (main effect of Synchrony: permutation p-value=0.0082, Fig.2B) and another bodily experience (Tab.S6), but did not modulate control items (all permutation p-values>0.08, Supplementary S18, Tab.S6). As for study1.2, riPH were not related to movement differences across conditions (permutation p-value=0.99) (Fig.2C), confirming that sensorimotor stimulation (and not movement differences) applied with the MR-compatible robot modulated PH intensity across conditions.

To identify the neural mechanisms of riPH, we determined brain regions that were (1) more activated during the asynchronous vs. synchronous condition (spatio-temporal sensorimotor conflict) and (2) activated by either of the sensorimotor conditions (synchronous, asynchronous) vs. two control conditions (motor and touch) (conjunction analysis, Supplementary S19). Conjunction analysis enabled us to capture the brain regions that reflect the spatial sensorimotor conflict between the sensorimotor movement of the hand in front space and the feedback in the back (Supplementary Fig.S4), which is independent of the right-hand movements (motor control), independent of the tactile feedback (touch control), and independent of whether asynchronous or synchronous stimulation was carried out. The asynchronous vs. synchronous contrast enabled us to detect changes related to the additional spatio-temporal contrast between the hand movement and the tactile feedback

(Supplementary S20, Fig.S4). Regions more activated during asynchronous vs. synchronous sensorimotor stimulation were restricted to cortical regions (Fig.2D, Tab.S7) and included the inferior frontal gyrus (IFG), anterior insula, medial prefrontal cortex (mPFC) and the posterior part of the middle temporal gyrus (pMTG, bordering on angular gyrus and adjacent occipital cortex). Conjunction analysis (between contrast synchronous>motor+touch and contrast asynchronous>motor+touch) (Supplementary S20, Fig.S5) revealed a subcortical-cortical network in left sensorimotor cortex (contralateral to the hand moving the robot, including M1, S1 and adjacent parts of premotor cortex and superior parietal lobule), in bilateral supplementary motor area (SMA), right inferior parietal cortex, left putamen, and right cerebellum (Fig.2E, Tab.S8).

Collectively, these fMRI results constitute the first delineation of the neural underpinnings of riPH in healthy participants that is unrelated to movement differences across conditions and distinct from activations in two control conditions, revealing a network of brain regions that have been shown to be involved in sensorimotor processing and in agency (such as M1-S1, pMTG (46, 47), PMC (48, 49), SMA (47, 50), IPS (51, 52), as well as the cerebellum (46, 53) and putamen).

Common PH-network for sPH and riPH (study2.2)

To determine neural similarities between riPH and sPH and confirm the sensorimotor contribution to sPH, we first applied lesion network mapping (Supplementary S21) and identified network connectivity mapping in neurological non-parkinsonian patients, in whom sPH were caused by focal brain damage (study2.2), and then determined the common network (cPH-network) between the riPH and sPH. Lesion network mapping (54) extends classical lesion symptom mapping by considering each lesion as a seed (region of interest, ROI) and computing its connectivity map (in normative resting state fMRI data, publicly available database, 126 healthy participants (55)) (Fig.S6).

This analysis revealed that all lesions had functional connectivity with bilateral posterior superior temporal gyrus/temporo-parietal junction (pSTG/TPJ), bilateral middle cingulate cortex (MCC), bilateral insula, and right IFG, constituting the sPH-network (Fig.3A, for all regions see Tab.S9) and did not overlap with connectivity patterns of a control hallucination network, in which the same method was applied to a control group of eleven patients

suffering from structured visual hallucinations (56) (Supplementary S22-S23, Tab.S10). We then determined whether there were any common brain regions between the sPH-network (non-parkinsonian neurological patients) and the riPH network (healthy participants). For this we performed an overlap between both networks, which identified the cPH-network consisting of three regions, including right IFG, right pMTG, and left vPMC (Fig.3B, Supplementary S24).

This is the first neuroimaging evidence that riPH and sPH recruit similar brain regions, even if both types of PH differ in several aspects such as frequency, intensity, trigger mechanism, supporting a link between sensorimotor robotics inducing hallucinatory states with neuroimaging in healthy participants and in patients. These data further corroborate that riPH and sPH are not related to tactile hallucinations by showing that the cPH-network does not include key tactile brain regions (e.g. SI), compatible with previous data for PH induced by invasive electrical stimulation (3) and lesion overlap analysis in neurological patients with sPH (insula and posterior temporo-parietal cortex (33).

Disrupted functional connectivity in cPH-network accounts for sPH Parkinson's disease (study3.1)

To assess the relevance of the cPH-network for PD patients' usual sPH in daily life, we analyzed resting state fMRI data in a new group of PD patients and investigated whether functional connectivity of the cPH-network (as defined in study2, projected bilaterally, Fig.3C) differed between PD-PH and PD-nPH (new cohort of 30 PD patients) (Supplementary S25-26, Tab.S11). Based on the disconnection hypothesis of hallucinations (57), evidence of decreased connectivity for hallucinations of psychiatric origin (40), and aberrant functional connectivity in PD patients with minor hallucinations including PH (27), we predicted that the functional connectivity within the cPH-network differs between both PD patient groups and that the connectivity within the cPH-network is reduced in PD-PH vs. PD-nPH patients. We found that the functional connectivity within the cPH-network, predicted with 93.7% accuracy whether a patient was clinically classified as PD-PH (kappa:0.86, permutation p-value=0.0042). Moreover, within the cPH-network, the functional connectivity between the left IFG and left pMTG contributed mostly to the classification of the two sub-groups (Tab.S12). PD-PH had reduced IFG-pMTG connectivity (permutation p-value<0.0001; Fig.4A-B). These changes were selective because (1) the same analysis in a control network (Fig.S8) (same size, same number

of connections) did not predict the occurrence of hallucinations based on the functional connectivity (accuracy:27.7%, kappa:-0.43, permutation p-value=0.24) and (2) no changes in functional connectivity were observed when analyzing whole brain connectivity. The difference in connectivity between PD-PH and PD-nPH cannot be explained by differences in demographic or clinical variables (including anti-parkinsonian medication, motor impairment, gender, neuropsychology, or cognitive functions, all permutation p-values>0.05). These data show that reduced fronto-temporal connectivity within the cPH-network distinguishes PD patients with sPH from those without hallucinations, in accordance with the disconnection hypothesis of hallucinations (57–59).

Functional disconnection within the cPH-network correlates with cognitive decline for PD-PH (study3.2).

It has been suggested that PH (and minor hallucinations) are indicative of a more severe and rapidly advancing form of PD, evolving towards structured visual hallucinations and psychosis (11, 60), as well as faster cognitive deterioration including dementia (17, 61–63). We therefore tested whether functional connectivity between the left IFG and the left pMTG within the cPH-network relates to cognitive dysfunction in the present PD-PH patients. Results show that stronger decreases in left IFG-pMTG connectivity are associated with stronger cognitive decline (PD-CRS (64)), reflecting differences in frontal-subcortical function (p-value=0.01,rho=0.69,Fig.4C), but not on posterior-cortical function (p-value=0.66, rho=-0.15, the two correlations differ significantly: t=3.87, p-value<0.01). These results reveal an association between fronto-subcortical cognitive alterations and specific decreases in fronto-temporal connectivity within the cPH-network in PD-PH patients, compatible with a more severe form of PD associating PH and cognitive decline.

General Discussion

Having developed a robotic procedure that can induce PH in PD patients under safe and controlled sensorimotor conditions, we report that PD patients with sPH are highly sensitive to the procedure and reveal abnormal sensorimotor mechanisms leading to PH. Using MR-compatible robotics in healthy participants combined with lesion network mapping analysis in patients with sPH of neurological non-parkinsonian origin, we identify the common network associated with PH and show that fronto-temporal connectivity within this cPH-network is selectively disrupted in a new and independent sample of PD patients. Disruption of the cPH-network was only found in PD patients suffering from sPH (PD-PH) and the degree of this disruption further predicted the severity of cognitive decline.

The present behavioural findings show that stronger sensorimotor conflicts result in stronger riPH, supporting and extending previous evidence in favor of an alteration of self-related sensorimotor processing as a fundamental mechanism underlying PH (28, 38). Importantly, we show that this mechanism is especially vulnerable in PD-PH patients, revealed by their stronger bias and sensitivity when exposed to conflicting sensorimotor stimulation. These results extend the sensorimotor forward model to presence hallucinations in PD-PH patients (39, 40, 43) and support earlier evidence in neurological non-PD patients that have classified PH among disorders of body schema and have further associated PH with altered sensorimotor self-monitoring (7–9). Altered sensorimotor monitoring has also been reported in psychosis research in psychiatric patients, suggesting that hallucinations are based on aberrant sensorimotor processes (e.g. 34, 40, 41) leading to a misattribution of self-generated actions to others (i.e. patients' failure to ignore irrelevant stimuli that result from one's own actions are erroneously processed as being externally generated).

By including fMRI data from healthy participants experiencing riPH and from non-parkinsonian neurological patients with sPH, we mapped common brain structures between both types of PH, which we showed to be selectively disrupted in PD patients with sPH. The imaging results within this cPH-network further revealed aberrant functional connectivity decreases between fronto-temporal regions that have been associated with outcome processing of sensorimotor signals and the forward model (59, 65), further linking PH in PD to the fronto-temporal hallucination disconnection model (57, 59, 66) that has associated

hallucinations with aberrant sensorimotor processes and a disruption of fronto-temporal communication (e.g. 67, 68).

Although not tested directly, we argue that the present PH-network and reported disruption may also be of relevance for PD patients suffering from other minor hallucinations or structured visual hallucinations. Thus, the implication of the pMTG in PD-PH patients, as highlighted by the results of Study 2 and 3, is in line with previous work showing impairments within the dorsal attentional networks and DMN for minor hallucinations (27) and structured visual hallucinations (69, 70) that have both been shown to involve the pMTG region. More brain imaging work and longitudinal studies in PD patients are needed, directly investigating the potential common and distinct brain networks involved in PH and visual hallucinations, especially with respect to attentional and DMN networks.

Our finding that the decreased fronto-temporal connectivity within the cPH-network is associated with stronger cognitive decline of PD-PH patients in fronto-subcortical (but not posterior-cortical, functions) lends support to clinical suggestions about the importance of PH (and other minor hallucinations) as a major risk factor not only for the occurrence of structured visual hallucinations and psychosis (60), but also for a more severe and rapidly advancing form of PD (11, 17, 61, 63). Because the phenomenology of riPH resembles those of sPH and PD-PH patients were found to be more sensitive to the present riPH procedure, the present procedure provides researchers and clinicians with new objective possibilities to assess the occurrence and intensity of subjective hallucinatory phenomena by quantifying delay-sensitivity and the repeated online induction of hallucinatory states across controlled conditions in PD patients, as well as the association of these measures with cPH-network activity. This is not possible in current clinical practice that is based on clinically important, but post-hoc interviews between physician and patient, often about hallucinations that have occurred many days or weeks ago, and that many patients hesitate to speak about (20). The detection of specific behavioural and imaging changes associated with specific hallucinatory states that are observed online during the robotic procedure will improve the quantification and prediction of a patient's proneness for PH, potentially for other hallucinations and psychosis, and may facilitate targeted pharmacological interventions that limit side effects (71).

Methods

Study 1

Participants (study1.1-1.2)

All participants provided written informed consent prior to the experiments. The study was approved by the Cantonal Ethics Committee of Geneva (Commission Cantonale d'Ethique de la Recherche sur l'Être Humain), the Cantonal Ethics Committee of Vaud. Participants of study1 consisted of patients with PD (n=26) and age-matched healthy controls (HC, n=21) (Supplementary S1-S4). Based on an extensive semi-structured interview (conducted after the experimental sessions) about hallucinations (including sPH), PD patients were separated into two sub-groups: patients who reported sPH as part of their PD (PD-PH) (n=13) and PD patients without sPH (PD-nPH) (n=13). Patients were considered as having sPH if they answered affirmatively to the question that previous investigators have used: "do you sometimes feel the presence of somebody close by when no-one is there?" The hallucinated presence could be located behind, on the side (left or right) of the patient, or in another room and was generally not seen (see (2, 7, 8, 10, 33)). All PD patients, who were included in study1 presented idiopathic PD diagnosed by trained neurologists. No patient was suffering from a neurological disorder other than PD (more details in Supplementary S2).

General experimental procedure (study1)

Each PD patient underwent study1 at a similar time (10am), after having received their usual anti-parkinsonian medication and were in their "best ON" state. To investigate riPH, we adapted the experimental method and device as our previous research (33). Briefly, sensorimotor stimulation was administered with a robotic system consisting of two robotic components (front-robot, back-robot) that has previously been used to induce PH. For each experimental session, we applied the following conditions: synchronous sensorimotor stimulation (the participants were asked to move the front-robot via either their right or left hand that was actuating the movements of the back-robot to apply tactile feedback to their back); asynchronous sensorimotor stimulation (same as synchronous stimulation, but with an additional temporal delay between the front-robot and the back-robot; see below for details of each experiment; Fig.1A). During sensorimotor stimulation, participants were always asked

to keep their eyes closed and were exposed to continuous white noise through headphones (Supplementary S3).

Procedure, design, and analysis (study1.1)

Participants were asked to insert their index finger in the haptic front-robot and carry out repeated poking movements while they received tactile cues on their backs, delivered by the back-robot. Thus, sensorimotor stimulation included motor, tactile, and proprioceptive signals from the upper limb moving the front-robot and additional tactile signals from the back-robot. Stroking was applied either synchronously (0ms delay) or asynchronously (500ms delay) (Synchrony: asynchronous vs. synchronous). Additionally, we measured the effect of the side of the body (i.e. hand moving the front-robot) that was most strongly affected by PD versus the other hand (Side) to investigate if the hemisphere predominantly affected by PD influenced riPH (72, 73). The factors (Synchrony; Side) and the order of testing were randomized across participants. Each participant randomly started with one Side first, for which the two Synchrony conditions (random order) were tested, and then the second Side was tested with the two Synchrony conditions (random order). In total, each participant performed four sessions (one per condition) lasting two minutes each. At the end of each of the four sensorimotor stimulation conditions, all participants filled a questionnaire (see below). Each PD-PH, PD-nPH, and HC included in the study was able to perform the entire study1.1.

PH and other subjective ratings

To measure PH and other illusions, we administered a questionnaire (6 questions) that was adapted from(33). Participants were asked to indicate on a 7-point Likert scale, how strongly they felt the sensation described by each item (from 0 = not at all, to 6 = very strong). For questions see Supplementary S5.

Data analysis

Each question was analyzed with linear mixed effects models (lme4 and lmerTest both R packages (74, 75)). Models were performed on the subjective ratings in each of the four conditions with Synchrony (synchronous vs. asynchronous), Groups (i.e., PD-PH vs. PD-nPH, and PD-PH vs. HC) and Side as fixed effects, and random intercepts for each subject. The

significance of fixed effects was estimated with a permutation test (5000 iterations; predictmeans (76) R package).

Procedure, design, and analysis (study1.2)

To complement and extend study1.1, we applied a Yes/No task, following sensorimotor stimulation, in which participants were asked to report whether they experienced a PH or not, on a trial-by-trial basis. On each sensorimotor stimulation trial, the delay between the movement and the stroking on the back was randomly chosen from a delay between 0 and 500ms (steps of 100m). One trial started with an acoustic signal (400 Hz tone, 100ms duration) indicating the beginning of the trial: at this point the participant started with the poking movements. Once the number of pokes reached a total of six (automatically counted), two consecutive tones (400 Hz, 100ms duration) indicated to the participant to stop the movements and to verbally answer with either a "Yes" or a "No" to the PH question, (Question: "Did you feel as if someone was standing close by (behind you or on one side)?"). The investigators where always placed > 4 meters away and in front from the participants during the experiment. Each participant was asked to perform three sessions; each session consisted of 18 trials (3 repetitions per delay (9 repetitions in total)). Between each session, the participant could take a break according to his/her needs (Supplementary S10).

riPH rating analysis

First, to investigate how the degree of sensorimotor conflict modulates PH, we analyzed the behavioral responses as a function of different delays (i.e., 0-500ms, steps of 100ms) across groups (i.e., PD-PH vs. PD-nPH). Here, the data was analyzed with a linear model, fitted for each participant independently. We assessed (1) the main effect of the delay (on the intensity of riPH) with a permutation test (5000 iterations) between slopes of the individual fit vs. zero; (2) the difference between the slopes of PD-PH vs. PD-nPH with a permutation test between the slopes of the two subgroups; (3) the main effect of group with a permutation test on the intercepts between the two subgroups.

Study 2

Participants, ethics, and informed consent (study2.1)

All healthy participants had no history of neurological or psychiatric disorders. All participants provided written informed consent prior to the experiment. The study was approved by the Cantonal Ethics Committee of Geneva (Commission Cantonale d'Ethique de la Recherche sur l'Être Humain - CCER). Twenty-five healthy participants (10 women, mean age±SD: 24.6±3.7 years old; age range: 18-32 years old, Edinburg Handedness Inventory mean index: 64.8±23.7 and range: 30-100) took part in study2.1.

Experimental procedure (study2.1)

The experimental procedure was based on a pilot study performed in a mock scanner (Supplementary S16). Participants were blindfolded during the task and received auditory cues through earphones to start (1 beep) and to stop (2 beeps) the movement. The paradigm was implemented using an in-house software (ExpyVR, http://lnco.epfl.ch/expyvr) and Visual studio 2013 interface (Microsoft) was used to control the robotic system.

Participants underwent two runs of 12 min each, during which they repeatedly had to move the front robot for 30s with their right hand followed by 20s of rest for a total of 16 repetitions per condition (8 repetitions for the motor and touch control tasks) (Supplementary S15-S19 and Fig.S3). Synchronous and the asynchronous conditions were randomized across runs. The questionnaire was presented at the end of the scanning session and after a randomized repetition of 30s of each condition. The questionnaire was based on the pilot study (Supplementary S16-S18) and on a previous study(33). Participants were asked to indicate on a 7-point Likert scale, how strongly they felt the sensation described by each item (from 0 = not at all, to 6 = very strong).

Questionnaire analysis

Questionnaire data were analyzed in the same way as in study1.1. Synchrony (synchronous and asynchronous) was used as a fixed effect and the subjects as random intercepts.

fMRI experiment

fMRI data acquisition

The imaging data was acquired with a 3T Siemens Magnetom Prisma MR scanner at Campus Biotech MR Platform (Geneva). The functional data were acquired using an Echo Planar Imaging (EPI) sequence with a full brain coverage (43 continuous slices, FOV=230mm, TR=2.5s,

TE=30ms, flip angle=90°, in-plane resolution=2.5x2.5mm2, slice thickness=2.5mm using a 64-channel head-coil) containing 320 volumes for the experimental runs and 160 volumes for the localizer runs. For each participant, an anatomical image was recorded using a T1-weighted MPRAGE sequence (TR=2.3s, TE=2.32 ms, Inversion time=900ms, flip angle=8°, 0.9mm isotropic voxels, 192 slices per slab and FOV=240mm).

fMRI data analysis

All the fMRI data analysis reported were pre-processed using SPM12 toolbox (Wellcome Department of Cognitive Neurology, Institute of Neurology, UCL, London, UK) in Matlab (R2016b, Mathworks). Slice timing correction and spatial realignment was applied to individual functional images. The anatomical image was then co-registered with the mean functional image and segmented into grey matter, white matter and cerebro-spinal fluid (CSF) tissue. Finally, the anatomical and the functional images were normalized to the Montreal Neurological Institute (MNI) brain template. Functional images were then smoothed with a Gaussian kernel with full-width half-maximum of 6mm. Head motion was assessed based on framewise displacement (FD) calculation (77). All participants had a mean FD value inferior to 0.50mm (mean FD=0.12±0.05 mm). The two experimental runs were filtered with a high-pass filter at 1/300 Hz to remove low frequency confounds, while the two localizers were filtered with a high-pass filter at 1/100 Hz.

Activation contrasts

The experimental runs and functional localizers were submitted to a general linear model (GLM) analysis. In all runs, the periods corresponding to a given robotic stimulation (i.e., synchronous, asynchronous, motor task, touch task (Supplementary S19 and Fig.S3)) and the periods corresponding to the auditory cues were modelled as separated regressors. The six realignment parameters were modelled for each run as regressors of no interest. In order to avoid confounding effects due to the amount of movement performed in each trial, the quantity of movement of the front robot (synchronous and asynchronous for the experimental runs and movement condition for the motor localizer, see above) was included as parametric modulators of each condition (see above).

Second-level analyses were performed using the first-level contrasts defined for each subject. In order to determine which brain regions were involved in sensorimotor conflicts (spatio-

temporal conflict and fixed spatial conflict), the following contrasts were computed: asynchronous>motor+touch and synchronous>motor+touch. A conjunction between those two contrasts was performed to identify the regions involved in the fixed spatial sensorimotor conflicts. For the experimental runs, two sample t-tests (asynchronous>synchronous and synchronous>asynchronous) were performed to assess brain activations activated during a specific sensorimotor conflict. Results were thresholded at $p<0.001$ at voxel level and only the clusters surviving $p<0.05$ FWE-corrected for multiple comparison were reported as significant. The obtained clusters were labelled using the AAL atlas (78) and the Anatomy toolbox(79).

Lesion network mapping analysis (study2.2)

In order to identify the brain regions functionally connected to each lesion location causing PH in neurological patients, we used lesion network mapping analysis (54, 80). Briefly, this method uses normative resting state data from 151 healthy subjects obtained from the publicly available Enhanced Nathan Kline Institute Rockland Sample (55) and uses the lesion locations as seed ROI. The fMRI acquisition parameters are described in the Supplementary S21.

Resting state fMRI analysis

For the pre-processing steps see above and Supplementary S21. The anatomical T1-weighted image was segmented into grey and white matter and CSF. Spatial realignment was applied to individual functional images. The six realignment parameters and their first-degree derivatives were added in addition to the averaged signals of the white matter and cerebro-spinal fluid. Subjects with the excessive motion were excluded from the analysis, this comprised 25 subjects which had a mean FD higher than 0.5mm and where more than 15% of scans were affected by movement. In total, 126 subjects were included for the analysis. Then, fMRI data was bandpass-filtered in the range of 0.008-0.09Hz.

The resting state data was analyzed using the CONN-fMRI Functional Connectivity toolbox (81) (v.18.a, http://www.nitrc.org/projects/conn). The lesion masks were used as seed ROIs and their mean time course was extracted and correlated to all other brain voxels. Each lesion-seed yielded a brain network thresholded at $p<0.001(t\pm3.37)$ with $p<0.05$ whole brain FWE peak level corrected. The 11 networks were then binarized and overlapped to determine the regions of shared positive and negative correlations (Fig.S6). The network overlap was

thresholded at 90% (at least 10 cases out of 11) with a minimal cluster extent of 50 voxels. This procedure was repeated with the structured visual hallucinations lesions (Supplementary S22-S23 for further analyses).

Study 3

Participants (study3.1)

Data from thirty PD patients were analyzed in this study. All patients were prospectively recruited from a sample of outpatients regularly attending to the Movement Disorders Clinic at Hospital de la Santa Creu i Sant Pau (Barcelona) based on the fulfilling of MDS new criteria for PD. Informed consent to participate in the study was obtained from all participants. The study was approved by the local Ethics Committee. Patients were diagnosed by a neurologist with expertise in movement disorders. Each patient was interviewed regarding years of formal education, disease onset, medication history, current medications, and dosage (levodopa daily dose). Motor status and stage of illness were assessed by the MDS-UPDRS-III. All participants were on stable doses of dopaminergic drugs during the 4 weeks before inclusion. Patients were included if the hallucinations remained stable during the 3 months before inclusion in the study. No participant had used or was using antipsychotic medication (Supplementary S24). Details of image acquisition and data processing are in Supplementary S25.

Regions of interest

The cPH-network as defined in Study 2 (right posterior middle temporal gyrus (pMTG; x =54, y=-54, z=0), the right inferior frontal gyrus (IFG; x=51, y=18, z=29) and the left ventral premotor cortex (vPMC; x=-53, y=1, z=37) was transposed bilaterally to ensure that the cPH-network is not affected by any effects of movement-related laterality of activation observed in the riPH-networks (Fig.3B). Clusters were built using FSL (https://fsl.fmrib.ox.ac.uk/fsl/). A control network was derived by shifting each region (x±0/20; y+30; z-15) of the cPH-network (Fig.S8). This approach allowed controlling for the exact same shape and number of voxels as original cPH-network areas.

Whole brain connectivity

To investigate global functional connectivity differences between the patient groups, a hypothesis-free (voxel-to-voxel) approach using CONN toolbox was applied. During first-level voxel-to-voxel analysis the estimation of voxel-to-voxel functional bivariate correlation coefficients matrix within each subject were computed. From this voxel-to-voxel correlation matrix, the intrinsic connectivity contrast (ICC) was established (82). The ICC characterizes the strength of the global connectivity pattern between each voxel and the rest of the brain (83). Briefly, the ICC is based on network theory's degree metric, which represents the number of voxels showing a correlation with each other voxel. Therefore, a whole-brain map is produced wherein the intensity of each voxel reflects the degree to which that voxel is connected to the rest of the brain. A greater ICC score represents greater average strength of the correlations in a given voxel. We compared PD-PH vs. PD-nPH. The correction of $p<0.001$ voxel level uncorrected and $p<0.05$ FDR cluster level corrected were applied.

Statistical analyses

To assess whether the functional connectivity of the cPH-network predicted if a patient was clinically classified PD-PH (or PD-nPH), we conducted a leave one out cross-validation procedure with a linear discriminant analysis (LDA) (using Caret R packages81). To ensure that the kappa value was above chance-level we conducted a permutation test (5000 iterations). At each iteration, functional connectivity values were permuted between sub-groups and the cross-validation procedure was repeated. Post-hoc analyses for the between group differences were performed using a permutation tests (5000 iterations) on the connection which mostly contributed to the decoding. Connectivity outliers (8.75% of all data points) were identified based on 1.5 IQR from the connectivity median value for each connection. Spearman 2-tailed correlation analyses were performed between functional connectivity within cPH-network areas and neuropsychological measures of the PD-CRS (Parkinson's disease – Cognitive Rating Scale). Significance between the two correlations was assessed using the Steiger Tests (psych R package (86)).

Code & Data availability

Matlab and R code are available on https://gitlab.epfl.ch/fbernasc/sensorimotor_hallucinations_pd.git; behavioral and MRI data are available on zenodo.org (project title "Sensorimotor hallucinations in Parkinson's Disease")

Figures

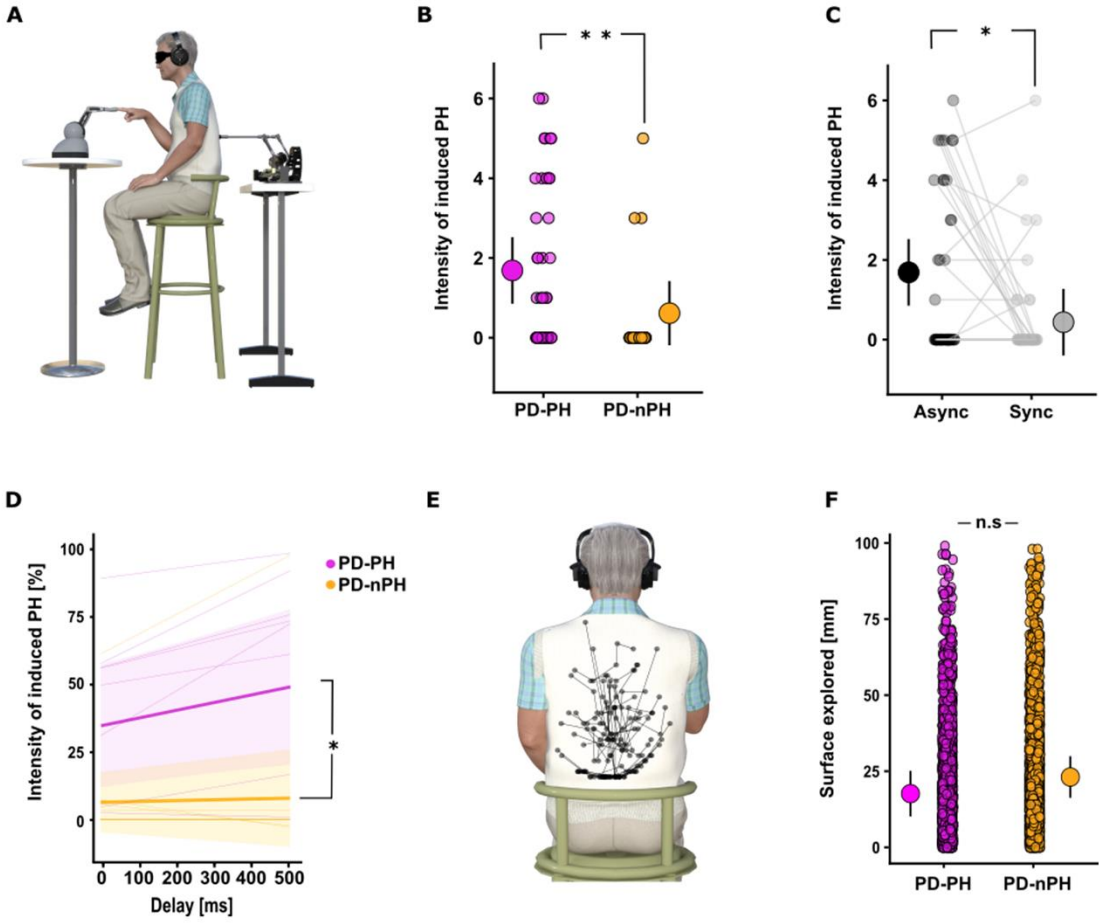

Figure 1. Robot-induced PH (PD patients). A. Setup for study 1. Responses in synchronous and asynchronous conditions are shown. During the asynchronous condition, the sensorimotor feedback on the participants' back was delayed by 500 ms (study1.1) or with a random delay (0-500ms, steps of 100ms) (study1.2). B. Study1.1. riPH in PD-PH are stronger than in PD-nPH. Each dot indicates the individual rating of the intensity of the riPH (PD-PH (purple) and PD-nPH (yellow)). The dot with the bar on the left and right side indicate the mixed effects linear regression between PD-PH and PD-nPH. Error bar represent 95% confidence interval. C. Study1.1. Asynchronous condition induced stronger riPH. Each dot indicates the individual rating of the intensity of the riPH. The dot with the bar on the left and right side indicate the mixed effects linear regression between Asynchronous (black) and Synchronous (gray) sensorimotor stimulation. Error bars represent 95% confidence interval. D. Study1.2. riPH were modulated by delay (permutation p-value=0.014) and PD-PH vs. PD-nPH were more sensitive to the sensorimotor stimulation (slope permutation p-value=0.039, intercept p-value=0.016). The thicker line indicates the mean of the fitted models, the shaded are indicates the 95% confidence interval, thinner lines indicate single subject fit. E. Study1.2. Exemplary movements executed by one patient during sensorimotor stimulation. F. Study1.2. Mixed effects linear regression between the Euclidean distance between pokes for PD-PH (purple) and PD-nPH (yellow). Error bar represent 95% confidence interval.

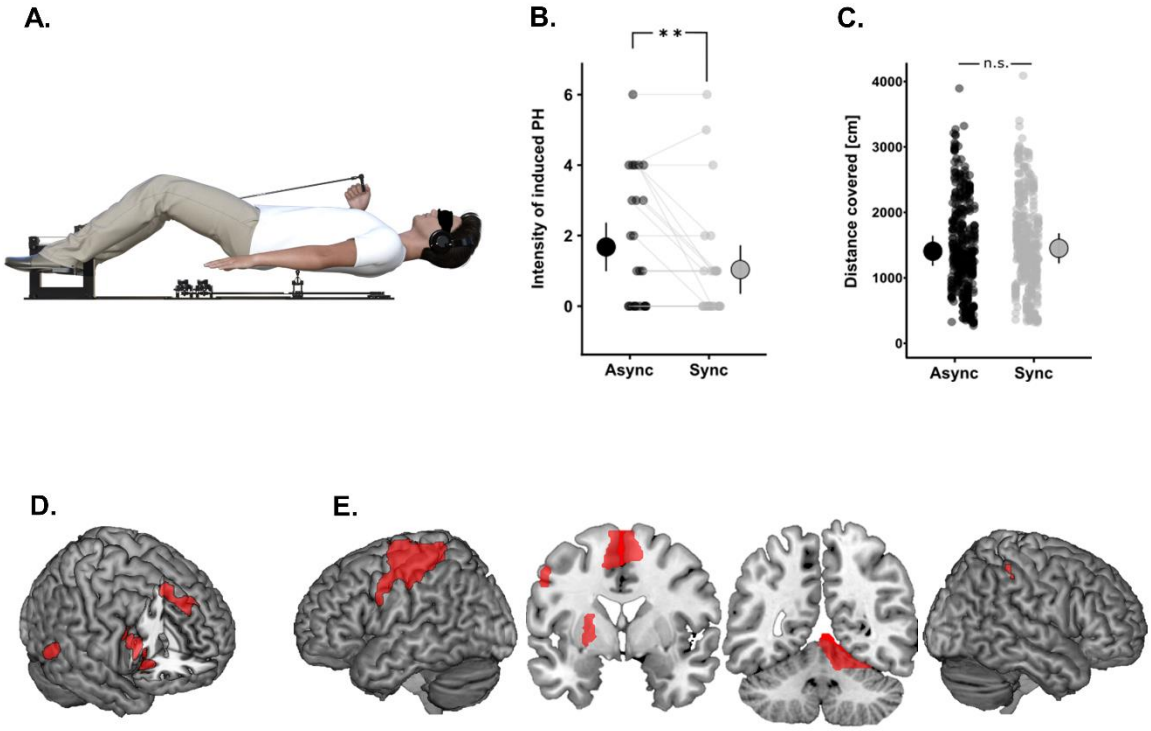

Figure 2. Neuroimaging results of robot-induced PH (healthy participants). A. MR-compatible robotic system is shown. Participants were instructed to move the front robot with their right hand and the back robot delivered the touch to the participant's back either synchronously or asynchronous (500ms delay between their movement and the sensory feedback received on the back). B. Asynchronous vs. synchronous condition induced stronger riPH. Each dot indicates the individual rating of the intensity of the riPH in healthy participants. The dot with the bar on the left and right side indicate the mixed effects linear regression between asynchronous (black) and synchronous (gray) sensorimotor stimulation. Error bar represents 95% confidence interval. C. Movement data from the fMRI experiment: no movement differences were found between the two conditions. D. Brain regions sensitive to the delay. E. Brain areas present in the conjunction analysis between the contrast synchronous>motor+touch and the contrast asynchronous>motor+touch. The coronal slices are at Y = -1 and Y = -53. There was no anatomical overlap between both networks (D and E).

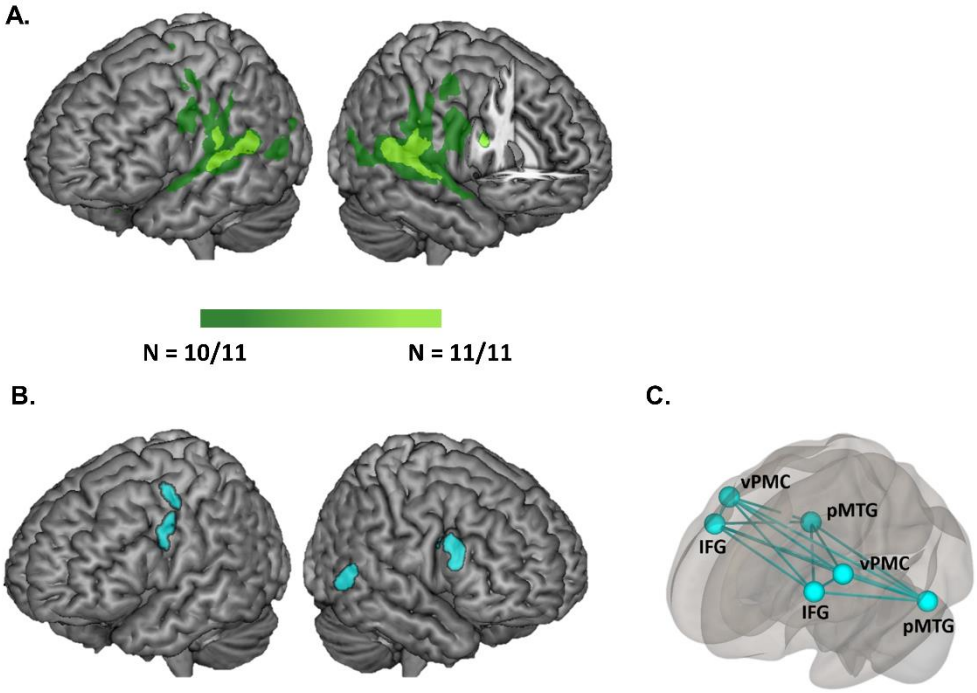

Figure 3. Symptomatic PH-network and common PH-network. A. MR-compatible robotic system is shown. Participants were instructed to move the front robot with their right hand and the back robot delivered the touch to the participant's back either synchronously or asynchronous (500ms delay between their movement and the sensory feedback received on the back). B. Asynchronous vs. synchronous condition induced stronger riPH. Each dot indicates the individual rating of the intensity of the riPH in healthy participants. The dot with the bar on the left and right side indicate the mixed effects linear regression between asynchronous (black) and synchronous (gray) sensorimotor stimulation. Error bar represents 95% confidence interval. C. Movement data from the fMRI experiment: no movement differences were found between the two conditions. D. Brain regions sensitive to the delay. E. Brain areas present in the conjunction analysis between the contrast synchronous>motor+touch and the contrast asynchronous>motor+touch. The coronal slices are at Y = −1 and Y = −53. There was no anatomical overlap between both networks (D and E).

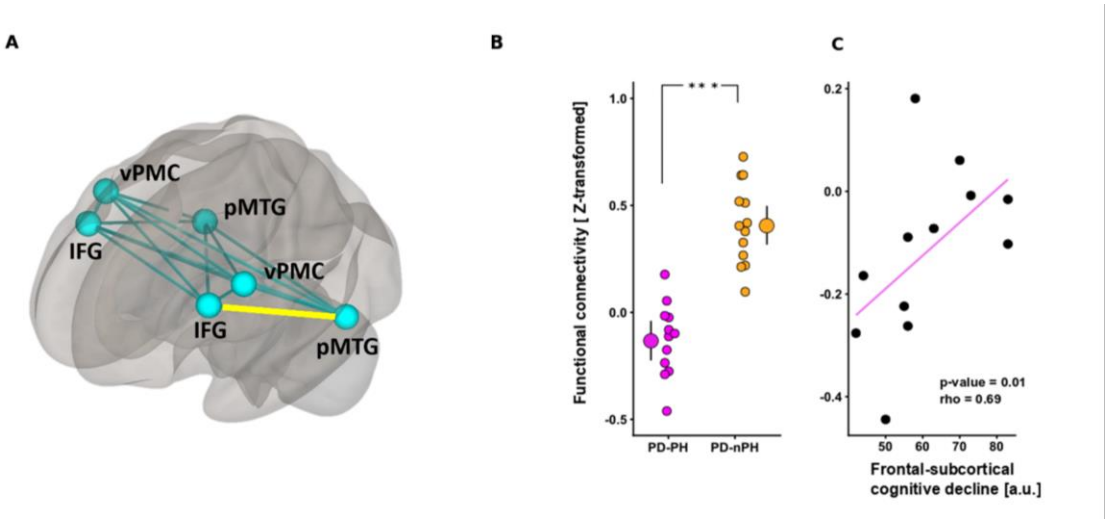

Figure 4. Functional connectivity in the sensorimotor network. A. Connections showing differences in functional connectivity between PD-PH vs. PD-nPH within the cPH-network are shown (yellow). B. Mixed effects linear regression between the functional connectivity for PD-PH (purple) and PD-nPH (yellow) between left IFG and left pMTG is shown. PD-PH vs. PD-nPH patients have a significantly reduced functional connectivity. Error bar represents 95% confidence interval, and the dot represents the mean functional connectivity. Dots represent the functional connectivity for each patient. C. Degree of functional disconnection is correlated with the cognitive decline (fronto-cortical sub-score of PD-CRS) in PD-PH patients. Lower connectivity was correlated with lower frontal cognitive fronto-subcortical abilities.

References

1. K. Jaspers, Über leibhaftige Bewusstheiten (Bewusstheitstaüschungen), ein psychopathologisches Elementarsymptom. Zeitschrift für Pathopsychologie. 2, 150–161 (1913).
2. M. Critchley, THE IDEA OF A PRESENCE. Acta Psychiatrica Scandinavica. 30, 155–168 (1955).
3. S. Arzy, M. Seeck, S. Ortigue, L. Spinelli, O. Blanke, Induction of an illusory shadow person. Nature. 443, 287 (2006).
4. R. Messner, The Naked Mountain (Seattle: Cambridge University Press, 2003).
5. J. Geiger, The Third Man Factor: Surviving the Impossible (New York: Weinstein Books, 2009).
6. P. M. Llorca, B. Pereira, R. Jardri, I. Chereau-Boudet, G. Brousse, D. Misdrahi, G. Fénelon, A.-M. Tronche, R. Schwan, C. Lançon, A. Marques, M. Ulla, P. Derost, B. Debilly, F. Durif, I. de Chazeron, Hallucinations in schizophrenia and Parkinson's disease: an analysis of sensory modalities involved and the repercussion on patients. Scientific Reports. 6, 38152 (2016).
7. P. Brugger, M. Regard, T. Landis, Unilaterally Felt "Presences": The Neuropsychiatry of One's Invisible Doppelgänger. Neuropsychiatry, neuropsychology, and behavioral neurology. 9, 114–122 (1996).
8. S. Arzy, M. Seeck, S. Ortigue, L. Spinelli, O. Blanke, Induction of an illusory shadow person. Nature. 443, 287 (2006).
9. M. Critchley, The divine banquet of the brain and other essays (Raven Press, 1979).
10. G. Fénelon, T. Soulas, L. C. De Langavant, I. Trinkler, A.-C. Bachoud-Lévi, Feeling of presence in Parkinson's disease. J Neurol Neurosurg Psychiatry. 82, 1219–1224 (2011).
11. A. Lenka, J. Pagonabarraga, P. K. Pal, H. Bejr-Kasem, J. Kulisvesky, Minor hallucinations in Parkinson disease: A subtle symptom with major clinical implications. Neurology (2019), doi:10.1212/WNL.0000000000007913.
12. D. H. Ffytche, B. Creese, M. Politis, K. R. Chaudhuri, D. Weintraub, C. Ballard, D. Aarsland, The psychosis spectrum in Parkinson disease. Nat Rev Neurol. 13, 81–95 (2017).
13. R. A. Wood, S. A. Hopkins, K. K. Moodley, D. Chan, Fifty Percent Prevalence of Extracampine Hallucinations in Parkinson's Disease Patients. Front Neurol. 6 (2015), doi:10.3389/fneur.2015.00263.
14. G. Fénelon, T. Soulas, F. Zenasni, L. C. De Langavant, The changing face of Parkinson's disease-associated psychosis: a cross-sectional study based on the new NINDS-NIMH criteria. Mov Disord. 25, 755–759 (2010).
15. N. J. Diederich, G. Fénelon, G. Stebbins, C. G. Goetz, Hallucinations in Parkinson disease. Nat Rev Neurol. 5, 331–342 (2009).
16. E. B. Forsaa, J. P. Larsen, T. Wentzel-Larsen, G. Alves, What predicts mortality in Parkinson disease?: a prospective population-based long-term study. Neurology. 75, 1270–1276 (2010).
17. J. Marinus, K. Zhu, C. Marras, D. Aarsland, J. J. van Hilten, Risk factors for non-motor symptoms in Parkinson's disease. The Lancet Neurology. 17, 559–568 (2018).
18. C. V. Kulick, K. M. Montgomery, M. J. Nirenberg, Comprehensive identification of delusions and olfactory, tactile, gustatory, and minor hallucinations in Parkinson's disease psychosis. Parkinsonism Relat. Disord. 54, 40–45 (2018).
19. H. H. Fernandez, D. Aarsland, G. Fénelon, J. H. Friedman, L. Marsh, A. I. Tröster, W. Poewe, O. Rascol, C. Sampaio, G. T. Stebbins, C. G. Goetz, Scales to assess psychosis in Parkinson's disease: Critique and recommendations. Movement Disorders. 23, 484–500 (2008).
20. B. Ravina, K. Marder, H. H. Fernandez, J. H. Friedman, W. McDonald, D. Murphy, D. Aarsland, D. Babcock, J. Cummings, J. Endicott, S. Factor, W. Galpern, A. Lees, L. Marsh, M. Stacy,

K. Gwinn-Hardy, V. Voon, C. Goetz, Diagnostic criteria for psychosis in Parkinson's disease: Report of an NINDS, NIMH Work Group. Movement Disorders. 22, 1061–1068 (2007).
21. S. Holroyd, L. Currie, G. F. Wooten, Prospective study of hallucinations and delusions in Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry. 70, 734–738 (2001).
22. R. S. Weil, A. E. Schrag, J. D. Warren, S. J. Crutch, A. J. Lees, H. R. Morris, Visual dysfunction in Parkinson's disease. Brain. 139, 2827–2843 (2016).
23. S. Davidsdottir, A. Cronin-Golomb, A. Lee, Visual and spatial symptoms in Parkinson's disease. Vision Res. 45, 1285–1296 (2005).
24. M. F. Silva, P. Faria, F. S. Regateiro, V. Forjaz, C. Januário, A. Freire, M. Castelo-Branco, Independent patterns of damage within magno-, parvo- and koniocellular pathways in Parkinson's disease. Brain. 128, 2260–2271 (2005).
25. D. J. Norton, A. Jaywant, X. Gallart-Palau, A. Cronin-Golomb, Normal discrimination of spatial frequency and contrast across visual hemifields in left-onset Parkinson's disease: Evidence against perceptual hemifield biases. Vision Research. 107, 94–100 (2015).
26. A. Jaywant, M. Shiffrar, S. Roy, A. Cronin-Golomb, Impaired Perception of Biological Motion in Parkinson's Disease. Neuropsychology. 30, 720–730 (2016).
27. H. Bejr-Kasem, J. Pagonabarraga, S. Martínez-Horta, F. Sampedro, J. Marín-Lahoz, A. Horta-Barba, I. Aracil-Bolaños, J. Pérez-Pérez, M. Ángeles Botí, A. Campolongo, C. Izquierdo, B. Pascual-Sedano, B. Gómez-Ansón, J. Kulisevsky, Disruption of the default mode network and its intrinsic functional connectivity underlies minor hallucinations in Parkinson's disease. Mov. Disord. 34, 78–86 (2019).
28. H Hecaen, De Ajuriaguerra, Misconstructions and hallucinations with respect to the body image; integration and disintegration of somatognosi. L' Evolution Psychiatrique (1952), pp. 745–750.
29. L. Weiskrantz, J. Elliott, C. Darlington, Preliminary observations on tickling oneself. Nature. 230, 598–599 (1971).
30. S. J. Blakemore, D. Wolpert, C. Frith, Why can't you tickle yourself? Neuroreport. 11, R11-16 (2000).
31. H. H. Ehrsson, N. P. Holmes, R. E. Passingham, Touching a rubber hand: feeling of body ownership is associated with activity in multisensory brain areas. J Neurosci. 25, 10564–10573 (2005).
32. P. Pozeg, G. Rognini, R. Salomon, O. Blanke, Crossing the Hands Increases Illusory Self-Touch. PLoS One. 9 (2014), doi:10.1371/journal.pone.0094008.
33. O. Blanke, P. Pozeg, M. Hara, L. Heydrich, A. Serino, A. Yamamoto, T. Higuchi, R. Salomon, M. Seeck, T. Landis, S. Arzy, B. Herbelin, Report Neurological and Robot-Controlled Induction of an Apparition. Current Biology. 24, 2681–2686 (2014).
34. S. S. Shergill, G. Samson, P. M. Bays, C. D. Frith, D. M. Wolpert, Evidence for sensory prediction deficits in schizophrenia. Am J Psychiatry. 162, 2384–2386 (2005).
35. S.-J. Blakemore, D. M. Wolpert, C. D. Frith, Central cancellation of self-produced tickle sensation. Nat Neurosci. 1, 635–640 (1998).
36. S.-J. Blakemore, D. M. Wolpert, C. D. Frith, Abnormalities in the awareness of action. Trends in Cognitive Sciences. 6, 237–242 (2002).
37. D. M. Wolpert, Z. Ghahramani, M. I. Jordan, An internal model for sensorimotor integration. Science. 269, 1880–1882 (1995).
38. R. C. Miall, D. M. Wolpert, Forward Models for Physiological Motor Control. Neural Networks. 9, 1265–1279 (1996).
39. P. R. Corlett, G. K. Murray, G. D. Honey, M. R. F. Aitken, D. R. Shanks, T. W. Robbins, E. T. Bullmore, A. Dickinson, P. C. Fletcher, Disrupted prediction-error signal in psychosis: evidence for an associative account of delusions. Brain. 130, 2387–2400 (2007).
40. P. C. Fletcher, C. D. Frith, Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. Nat. Rev. Neurosci. 10, 48–58 (2009).

41. J. M. Ford, D. H. Mathalon, Electrophysiological evidence of corollary discharge dysfunction in schizophrenia during talking and thinking. Journal of Psychiatric Research. 38, 37–46 (2004).
42. R. Salomon, P. Progin, A. Griffa, G. Rognini, K. Q. Do, P. Conus, S. Marchesotti, F. Bernasconi, P. Hagmann, A. Serino, O. Blanke, Sensorimotor Induction of Auditory Misattribution in Early Psychosis. Schizophr Bull (2020), doi:10.1093/schbul/sbz136.
43. A. Conte, N. Khan, G. Defazio, J. C. Rothwell, A. Berardelli, Pathophysiology of somatosensory abnormalities in Parkinson disease. Nature Reviews Neurology. 9, 687–697 (2013).
44. J. Pagonabarraga, C. Soriano-Mas, G. Llebaria, M. López-Solà, J. Pujol, J. Kulisevsky, Neural correlates of minor hallucinations in non-demented patients with Parkinson's disease. Parkinsonism & Related Disorders. 20, 290–296 (2014).
45. M. Hara, R. Salomon, W. van der Zwaag, T. Kober, G. Rognini, H. Nabae, A. Yamamoto, O. Blanke, T. Higuchi, A novel manipulation method of human body ownership using an fMRI-compatible master-slave system. Journal of Neuroscience Methods. 235, 25–34 (2014).
46. D. T. Leube, G. Knoblich, M. Erb, W. Grodd, M. Bartels, T. T. J. Kircher, The neural correlates of perceiving one's own movements. NeuroImage. 20, 2084–2090 (2003).
47. M. Sperduti, P. Delaveau, P. Fossati, J. Nadel, Different brain structures related to self- and external-agency attribution: a brief review and meta-analysis. Brain Struct Funct. 216, 151–157 (2011).
48. N. David, A. Newen, K. Vogeley, The '' sense of agency '' and its underlying cognitive and neural mechanisms. Consciousness and Cognition. 17, 523–534 (2008).
49. S. J. Blakemore, D. M. Wolpert, C. D. Frith, Central cancellation of self-produced tickle sensation. Nature neuroscience. 1, 635–640 (1998).
50. Y. Yomogida, M. Sugiura, Y. Sassa, K. Wakusawa, A. Sekiguchi, A. Fukushima, H. Takeuchi, K. Horie, S. Sato, R. Kawashima, The neural basis of agency: an fMRI study. Neuroimage. 50, 198–207 (2010).
51. H. H. Ehrsson, N. P. Holmes, R. E. Passingham, Touching a rubber hand: feeling of body ownership is associated with activity in multisensory brain areas. The Journal of neuroscience : the official journal of the Society for Neuroscience. 25, 10564–73 (2005).
52. C. Farrer, N. Franck, N. Georgieff, C. D. Frith, J. Decety, M. Jeannerod, Modulating the experience of agency: A positron emission tomography study. NeuroImage. 18, 324–333 (2003).
53. S. J. Blakemore, A. Sirigu, Action prediction in the cerebellum and in the parietal lobe. Experimental Brain Research. 153, 239–245 (2003).
54. A. D. Boes, S. Prasad, H. Liu, Q. Liu, A. Pascual-Leone, V. S. Caviness, M. D. Fox, Network localization of neurological symptoms from focal brain lesions. Brain. 138, 3061–3075 (2015).
55. K. B. Nooner, S. J. Colcombe, R. H. Tobe, M. Mennes, M. M. Benedict, A. L. Moreno, L. J. Panek, S. Brown, S. T. Zavitz, Q. Li, S. Sikka, D. Gutman, S. Bangaru, R. T. Schlachter, S. M. Kamiel, A. R. Anwar, C. M. Hinz, M. S. Kaplan, A. B. Rachlin, S. Adelsberg, B. Cheung, R. Khanuja, C. Yan, C. C. Craddock, V. Calhoun, W. Courtney, M. King, D. Wood, C. L. Cox, A. M. C. Kelly, A. Di Martino, E. Petkova, P. T. Reiss, N. Duan, D. Thomsen, B. Biswal, B. Coffey, M. J. Hoptman, D. C. Javitt, N. Pomara, J. J. Sidtis, H. S. Koplewicz, F. X. Castellanos, B. L. Leventhal, M. P. Milham, The NKI-Rockland Sample: A Model for Accelerating the Pace of Discovery Science in Psychiatry. Front Neurosci. 6 (2012), doi:10.3389/fnins.2012.00152.
56. L. Heydrich, O. Blanke, Distinct illusory own-body perceptions caused by damage to posterior insula and extrastriate cortex. Brain. 136, 790–803 (2013).
57. K. J. Friston, The disconnection hypothesis. Schizophr. Res. 30, 115–125 (1998).
58. K. Friston, H. R. Brown, J. Siemerkus, K. E. Stephan, The dysconnection hypothesis (2016). Schizophrenia Research. 176, 83–94 (2016).
59. C. Frith, The neural basis of hallucinations and delusions. C. R. Biol. 328, 169–175 (2005).

60. C. G. Goetz, W. Fan, S. Leurgans, B. Bernard, G. T. Stebbins, The malignant course of "benign hallucinations" in Parkinson disease. Arch. Neurol. 63, 713–716 (2006).
61. D. Aarsland, M. Hutchinson, J. P. Larsen, Cognitive, psychiatric and motor response to galantamine in Parkinson's disease with dementia. Int J Geriatr Psychiatry. 18, 937–941 (2003).
62. B. Ramirez-Ruiz, C. Junque, M.-J. Marti, F. Valldeoriola, E. Tolosa, Cognitive changes in Parkinson's disease patients with visual hallucinations. Dement Geriatr Cogn Disord. 23, 281–288 (2007).
63. L. Morgante, C. Colosimo, A. Antonini, R. Marconi, G. Meco, M. Pederzoli, F. E. Pontieri, G. Cicarelli, G. Abbruzzese, S. Zappulla, S. Ramat, M. Manfredi, E. Bottacchi, M. Abrignani, A. Berardelli, A. Cozzolino, C. Paradiso, D. De Gaspari, F. Morgante, P. Barone, PRIAMO Study Group, Psychosis associated to Parkinson's disease in the early stages: relevance of cognitive decline and depression. J. Neurol. Neurosurg. Psychiatry. 83, 76–82 (2012).
64. J. Pagonabarraga, J. Kulisevsky, G. Llebaria, C. García-Sánchez, B. Pascual-Sedano, A. Gironell, Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. Mov. Disord. 23, 998–1005 (2008).
65. S. J. Blakemore, C. Frith, Self-awareness and action. Curr. Opin. Neurobiol. 13, 219–224 (2003).
66. K. J. Friston, Theoretical neurobiology and schizophrenia. Br. Med. Bull. 52, 644–655 (1996).
67. S. M. Lawrie, C. Buechel, H. C. Whalley, C. D. Frith, K. J. Friston, E. C. Johnstone, Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations. Biol. Psychiatry. 51, 1008–1011 (2002).
68. G. Fénelon, T. Soulas, L. C. de Langavant, I. Trinkler, A.-C. Bachoud-Lévi, Feeling of presence in Parkinson's disease. J Neurol Neurosurg Psychiatry. 82, 1219–1224 (2011).
69. J. M. Shine, G. M. Halliday, M. Gilat, E. Matar, S. J. Bolitho, M. Carlos, S. L. Naismith, S. J. G. Lewis, The role of dysfunctional attentional control networks in visual misperceptions in Parkinson's disease. Hum Brain Mapp. 35, 2206–2219 (2014).
70. J. M. Shine, R. Keogh, C. O'Callaghan, A. J. Muller, S. J. G. Lewis, J. Pearson, Imagine that: elevated sensory strength of mental imagery in individuals with Parkinson's disease and visual hallucinations. Proc. Biol. Sci. 282, 20142047 (2015).
71. D. Weintraub, H. C. Kales, C. Marras, The Danger of Not Treating Parkinson Disease Psychosis-Reply. JAMA Neurol. 73, 1156–1157 (2016).
72. A. Q. Rana, H. M. Vaid, A. Edun, O. Dogu, M. A. Rana, Relationship of dementia and visual hallucinations in tremor and non-tremor dominant Parkinson's disease. J. Neurol. Sci. 323, 158–161 (2012).
73. J. S. a. M. Reijnders, U. Ehrt, R. Lousberg, D. Aarsland, A. F. G. Leentjens, The association between motor subtypes and psychopathology in Parkinson's disease. Parkinsonism Relat. Disord. 15, 379–382 (2009).
74. D. Bates, M. Mächler, B. Bolker, S. Walker, Fitting Linear Mixed-Effects Models Using lme4. Journal of Statistical Software. 67, 1–48 (2015).
75. A. Kuznetsova, P. B. Brockhoff, R. H. B. Christensen, lmerTest Package: Tests in Linear Mixed Effects Models. Journal of Statistical Software. 82, 1–26 (2017).
76. Luo, D, Ganesh, S, Koolaard, J, predictmeans: Calculate Predicted Means for Linear Models, http://cran.r-project.org/package=predictmeans (2014).
77. J. D. Power, K. A. Barnes, A. Z. Snyder, B. L. Schlaggar, S. E. Petersen, Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage. 59, 2142–2154 (2012).
78. N. Tzourio-Mazoyer, B. Landeau, D. Papathanassiou, F. Crivello, O. Etard, N. Delcroix, B. Mazoyer, M. Joliot, Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. NeuroImage. 15, 273–289 (2002).

79. S. B. Eickhoff, K. E. Stephan, H. Mohlberg, C. Grefkes, G. R. Fink, K. Amunts, K. Zilles, A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. NeuroImage. 25, 1325–1335 (2005).
80. M. D. Fox, Mapping Symptoms to Brain Networks with the Human Connectome. New England Journal of Medicine. 379, 2237–2245 (2018).
81. S. Whitfield-Gabrieli, A. Nieto-Castanon, Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2, 125–141 (2012).
82. R. Martuzzi, R. Ramani, M. Qiu, X. Shen, X. Papademetris, R. T. Constable, A whole-brain voxel based measure of intrinsic connectivity contrast reveals local changes in tissue connectivity with anesthetic without a priori assumptions on thresholds or regions of interest. Neuroimage. 58, 1044–1050 (2011).
83. M. E. Raichle, The restless brain. Brain Connect. 1, 3–12 (2011).
84. M. Kuhn, Astrophysics Source Code Library, in press.
85. J. Friedman, T. Hastie, R. Tibshirani, Regularization Paths for Generalized Linear Models via Coordinate Descent. J Stat Softw. 33, 1–22 (2010).
86. W. R. Revelle, psych: Procedures for Personality and Psychological Research (2017) (available at https://www.scholars.northwestern.edu/en/publications/psych-procedures-for-personality-and-psychological-research).

Supplementary Information

Study 1

Study 1.1: Robot-induced presence hallucinations (riPH) in patients with PD

Supplementary S1

Participants: Inclusion/Exclusion criteria

Participants in the present study consisted of patients with PD and the symptom of PH (PD-PH, n=13), patients with PD without the symptom of PH (PD-nPH, n=13), and age-matched healthy controls (HC, n=21). Demographic and clinical data are summarized in Table S1. Patients with cognitive impairments (defined as a MoCA score(1) lower then 24 (2)), treated with neuroleptics, affected by other central neurological co-morbidities, affected by psychiatric co-morbidities unrelated to PD, and patients with recent (< one month) changes in their medical treatment were not included in the study. The HC included in the study never experienced PH, did not suffer from a neurological or psychiatric disease, and had no objective sign of cognitive impairment.

Supplementary S2

Demographic and disease-related variables

For every PD patient, the doses of anti-parkinsonian medication were converted to the levodopa equivalent daily dose (3). The severity of motor symptoms was assessed by the score at the Movement Disorders Society - Unified Parkinson Disease Rating Scale (MDS-UPDRS) - part III (Goetz et al., 2008), in "ON" state. In addition, impulsive-compulsive disorders were assessed by the score at the "Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease" (QUIP-RS (4)). We also assessed for PD-PH, PD-nPH, and HC apathy scale (5) and the risk for psychosis (Prodromal Questionnaire PQ-16 (6); which was divided in part I (hallucinations, and negative symptoms-like experiences), and part II (level of distress linked to the experiences). Hallucinations were assessed with a semi-structured interview adapted from the psychosensory hallucinations Scale (PSAS) for Schizophrenia and Parkinson's disease (7). Next to PH, we also inquired about other hallucinations possibly experienced by patients with PD, e.g. passage hallucinations (i.e., animal, person or indefinite object passing in the peripheral visual field), visual illusion and complex hallucinations (structured visual, auditory or tactile hallucinations) as well as delusional ideas.

	PD-PH (N = 13)	PD-nPH (N = 13)	*p-values*
Age	60.69 ± 13.19	65.69 ± 7.60	0.25
Gender	9 (M)	4 (M)	0.05 (χ2)
UPDRS-III	20 ± 12.09	19 ± 17.51	0.87
MoCA	26.85 ± 1.82	28.15 ± 1.57	0.08
PQ16	4.00 ± 2.00	0.69 ± 1.32	< 0.001
PQ16-2	3.54 ± 4.86	1.08 ± 2.63	0.1
Apathy	12.69 ± 8.06	10.23 ± 4.64	0.37
LEDD (mg/day)	727.77 ± 410.46	786.23 ± 657.23	0.8
Disease Duration (years)	9.46 ± 4.22	9.38 ± 5.72	0.5

Table S1. Clinical variables between PD-PH and PD-nPH.

	PD-PH (N = 13)	HC (N = 21)	*p-values*
Age	60.69 ± 13.19	66.90 ± 5.75	0.06
Gender	9 (M)	11 (M)	0.9 (χ2)
MoCA	26.85 ± 1.82	28.52 ± 1.03	<0.001
PQ16	4.00 ± 2.00	0.24 ± 0.44	<0.001
PQ16-2	3.54 ± 4.86	0 ± 0	<0.001
Apathy	12.69 ± 8.06	6.33 ± 4.05	0.01

Table S2. Clinical variables between PD-PH and HC.

Supplementary S3

Experimental procedure

Each PD patient underwent study1 at a similar time (10am), after having received their usual anti-parkinsonian medication and were in their "best ON" state for the whole duration of study1 as well as the psychological and neuropsychological assessments(8). To investigate the riPH in patients with PD (and HC), we used the same experimental setup and device as our previous research (9). The robotic stimulation was administered through a robotic system (10) that has previously been used to induce the PH and other bodily illusions in healthy subjects

(9). The experimental design consisted in factors Synchrony (synchronous/asynchronous), Side (most/less affected) and Group (PD-PH/PD-nPH).

Supplementary S4

Questionnaire results: PH

Detailed ratings for all questions can be seen on Table S3 (below).

riPH ("I felt as if someone was close-by")

PD-PH vs. PD-nPH. No main effect of Side (permutation p-value=0.37). No interactions were observed, all permutation p-values>0.05.

By adding Gender as covariate to our analysis in Study 1, we observed again similar results to those reported before. Gender did not influence significantly the rating (permutation p-value = 0.6), and we confirm the enhanced sensitivity to the sensorimotor robotic stimulations (permutation p-value = 0.04, main effect of Group) and the importance of the conflicting sensorimotor stimulation to induced PH (permutation p-value = 0.028, main effect of Synchrony). MoCa score did not influence significantly the ratings (permutationp-value = 0.06), and we confirmed the enhanced sensitivity to the sensorimotor robotic stimulations (permutation p-value = 0.037, main effect of Group) and the importance of the conflicting sensorimotor stimulation to induced PH (permutation p-value = 0.038, main effect of Synchrony). In addition, this is in line with what we observed in Study 3, where Gender (p-value = 0.7) and MoCa (p-value = 0.3) were not statistically different between patients with and without PH.

PD-PH vs. HC. By comparing PD-PH and HC, we confirmed the importance of conflicting sensorimotor stimulation to induced PH, as both groups gave higher PH ratings in the asynchronous versus synchronous condition (permutation p-value=0.033, main effect of Synchrony). The intensity of riPH ratings did not differ statistically between PD-PH and HC (permutation p-value=0.48, main effect of Group). The Side did not significantly modulate the riPH ratings (permutation p-value=0.38, main effect of Side). No interactions were observed, all permutation p-values>0.05.

Supplementary S5

Questionnaire results: Other robot-induced perceptions

Passivity experience ("I felt as if someone else was touching my back.").

PD-PH vs. PD-nPH. The two sub-groups of patients did not report difference in passivity experiences in the asynchronous condition (permutation p-value = 0.1, main effect of Synchrony), the ratings did not differ significantly between the groups of patients (permutation p-value = 0.38, main effect of Group), and the Side did not modulate the passivity experience (permutation p-value=0.41, main effect of Side). No interactions were observed, all permutation p-values>0.05.

PD-PH vs. HC. We observed a trend for asynchronous condition to induce higher passivity experiences (permutation p-value=0.06, main effect of Synchrony). The ratings were not statistically different between the groups (permutation p-value=0.86, main effect of Group). The Side modulated the passivity experience (permutation p-value<0.01, main effect of Side). No interactions were observed, all other permutation p-values>0.05.

Self-touch ("I felt as if I was touching my back.").

PD-PH vs. PD-nPH. In line with previous work(9), the two sub-groups of patients reported higher self-touch experiences in the synchronous condition (permutation p-value=0.043, main effect of Synchrony). The ratings did not differ significantly neither between the groups of patients (permutation p-value=0.65, main effect of Group), nor between the Side (permutation p-value=0.51, main effect of Side). No interactions were observed, all other permutation p-values>0.05.

PD-PH vs. HC. We observed that participants reported a trend for higher self-touch experiences in the synchronous condition (permutation p-value=0.054, main effect of Synchrony). The rating did not differ significantly neither between the groups (permutation p-value=0.92, main effect of Group), nor between the Side (permutation p-value=0.4, main effect of Side). No interactions were observed (all other permutation p-values>0.05).

Loss of agency (“I felt as if I was not controlling my movements or actions.”).

PD-PH vs. PD-nPH. The robotic stimulation was associated with a stronger loss of agency in PD-PH than PD-nPH (permutation p-value=0.045, main effect of Group). Neither the sensorimotor condition (permutation p-value=0.26, main effect of Synchrony), nor the Side (permutation p-value=0.67, main effect of Side) modulated significantly the rating. No interactions were observed, all other permutation p-values>0.05.

PD-PH vs. HC. No statistical difference was observed between the two sub-groups (permutation p-value=0.073, main effect of Group). Neither the sensorimotor condition (permutation p-value=0.6, main effect of Synchrony) nor the Side (permutation p-value=0.28, main effect of Side) modulated significantly the ratings. No interactions were observed, all other permutation p-values>0.05.

Bodily sensations (“I felt as if I had two bodies”) (Control item 1).

PD-PH vs. PD-nPH. The robotic stimulation did not modulate significantly this bodily sensation (permutation p-value=0.98, main effect of Synchrony), we did not observe statistically significant differences between the two sub-groups (permutation p-value=0.26, main effect of Group), and did not observed a difference due to the Side (permutation p-value=0.88, main effect of Side). No interactions were observed, all other permutation p-values>0.05.

PD-PH vs. HC. The robotic stimulation neither modulated this bodily sensation (permutation p-value=0.85, main effect of Synchrony) nor did the two sub-groups (permutation p-value=0.79, main effect of Group), and we did not observe a difference due to the Side (permutation p-value=0.71, main effect of Side). No interactions were observed, all other permutation p-values>0.05.

Control Question (“I felt someone was standing in front of me.”) (Control item 2).

For each of the three sub-groups, all the raw ratings were zeros for the question front-PH (permutation p-value=1).

Question	Group	Synchrony	Side	Mean	Standard Deviation
PH	PD-PH	Async	Less affected side	1.67	2.31
PH	PD-PH	Async	Most affected side	2.23	2.17
PH	PD-PH	Sync	Less affected side	0.42	0.9
PH	PD-PH	Sync	Most affected side	1.31	1.93
PH	PD-nPH	Async	Less affected side	0.62	1.56
PH	PD-nPH	Async	Most affected side	0.23	0.83
PH	PD-nPH	Sync	Less affected side	0	0
PH	PD-nPH	Sync	Most affected side	0	0
PH	HC	Async	Less affected side	1.05	1.96
PH	HC	Async	Most affected side	1.33	2.15
PH	HC	Sync	Less affected side	0.52	1.66
PH	HC	Sync	Most affected side	0.86	1.93

Question	Group	Synchrony	Side	Mean	Standard Deviation
Loss of agency	PD-PH	Async	Less affected side	1.83	2.25
Loss of agency	PD-PH	Async	Most affected side	2.25	2.14
Loss of agency	PD-PH	Sync	Less affected side	1.17	1.7
Loss of agency	PD-PH	Sync	Most affected side	1.75	1.71
Loss of agency	PD-nPH	Async	Less affected side	0.85	1.63
Loss of agency	PD-nPH	Async	Most affected side	0.54	0.97
Loss of agency	PD-nPH	Sync	Less affected side	0.08	0.28
Loss of agency	PD-nPH	Sync	Most affected side	0.23	0.6
Loss of agency	HC	Async	Less affected side	0.48	1.25
Loss of agency	HC	Async	Most affected side	0.81	1.47
Loss of agency	HC	Sync	Less affected side	0.24	0.89
Loss of agency	HC	Sync	Most affected side	0.9	1.7

Question	Group	Synchrony	Side	Mean	Standard Deviation
Passivity experience	PD-PH	Async	Less affected side	2.33	2.31
Passivity experience	PD-PH	Async	Most affected side	3.08	2.43
Passivity experience	PD-PH	Sync	Less affected side	1.25	2.05
Passivity experience	PD-PH	Sync	Most affected side	2.08	2.14
Passivity experience	PD-nPH	Async	Less affected side	2.54	2.37
Passivity experience	PD-nPH	Async	Most affected side	1.77	2.05
Passivity experience	PD-nPH	Sync	Less affected side	1.54	2.22
Passivity experience	PD-nPH	Sync	Most affected side	1.38	1.94
Passivity experience	HC	Async	Less affected side	1.81	2.5
Passivity experience	HC	Async	Most affected side	3.29	2.31
Passivity experience	HC	Sync	Less affected side	1.29	2.22
Passivity experience	HC	Sync	Most affected side	2.33	2.61

Question	Group	Synchrony	Side	Mean	Standard Deviation
Self-touch	PD-PH	Async	Less affected side	1.92	2.35
Self-touch	PD-PH	Async	Most affected side	1.38	1.66
Self-touch	PD-PH	Sync	Less affected side	2.08	2.27
Self-touch	PD-PH	Sync	Most affected side	3	2.24
Self-touch	PD-nPH	Async	Less affected side	0.85	1.57
Self-touch	PD-nPH	Async	Most affected side	0.85	1.57
Self-touch	PD-nPH	Sync	Less affected side	1.46	2.37
Self-touch	PD-nPH	Sync	Most affected side	1.92	2.56
Self-touch	HC	Async	Less affected side	2.38	2.69
Self-touch	HC	Async	Most affected side	1.86	2.46
Self-touch	HC	Sync	Less affected side	2.43	2.84
Self-touch	HC	Sync	Most affected side	2.81	2.84

Question	Group	Synchrony	Side	Mean	Standard Deviation
PH front	PD-PH	Async	Less affected side	0	0
PH front	PD-PH	Async	Most affected side	0	0
PH front	PD-PH	Sync	Less affected side	0	0
PH front	PD-PH	Sync	Most affected side	0	0
PH front	PD-nPH	Async	Less affected side	0	0
PH front	PD-nPH	Async	Most affected side	0	0
PH front	PD-nPH	Sync	Less affected side	0	0
PH front	PD-nPH	Sync	Most affected side	0	0
PH front	HC	Async	Less affected side	0	0
PH front	HC	Async	Most affected side	0	0
PH front	HC	Sync	Less affected side	0	0
PH front	HC	Sync	Most affected side	0	0

Question	Group	Synchrony	Side	Mean	Standard Deviation
Control	PD-PH	Async	Less affected side	0.25	0.62
Control	PD-PH	Async	Most affected side	0.54	1.2
Control	PD-PH	Sync	Less affected side	0.25	0.87
Control	PD-PH	Sync	Most affected side	0.38	0.96
Control	PD-nPH	Async	Less affected side	0	0
Control	PD-nPH	Async	Most affected side	0	0
Control	PD-nPH	Sync	Less affected side	0	0
Control	PD-nPH	Sync	Most affected side	0	0
Control	HC	Async	Less affected side	0.19	0.87
Control	HC	Async	Most affected side	0.19	0.87
Control	HC	Sync	Less affected side	0	0
Control	HC	Sync	Most affected side	0.24	1.09

Table S3. Mean ratings for all questions, and experimental conditions

Supplementary S6

Post-experiment debriefing: riPH mimic sPH (in PD-PH)

Patients reports. One PD-PH patient reported that he could feel the robot-induced presence on the side (not on the back) and added (after being asked to compare s- and riPH) “it is slightly similar, but it is not exactly the same because the presence (symptomatic) is all of a sudden, while here (the riPH) it is built-up”. Although, the riPH was strong felt, another PD-PH patient noted that the PH lacked some aspects of his symptomatic PH (sPH). He described that “when I feel the symptomatic PH it’s like a chewing gum with a lot of taste, while here (the riPH) it was still like chewing gum but without the taste”. Another PD-PH patient compared his riPH to “an adrenaline rush. Like something or someone was behind me, although there is not the possibility to have someone behind” and “I really had the impression that someone was doing something behind me”. Another PD-PH patient reported that “I honestly have the impression to have someone behind me”. Just after the stimulation and removal of the blindfold she added “I was surprised to see you all in front of me”.

Supplementary S7

Post-experiment debriefing: Spatial location of the riPH

We further determined the experienced spatial location of the riPH and whether this differed across the three participant groups. Analyzing all trials for which a participant positively rated the PH during the robotic procedure (i.e., value > 0 on Likert scale) we found that PD-PH patients reported a higher number of lateralized riPH (n=24; i.e. instances of a riPH with a value > 0; across all trials and conditions) then HC (n=18) (Chi-square: p-value = 0.003, $\chi^2(1)=9$) and PD-nPH (n=3) (Chi-square: p-value = 0.001, $\chi^2(1)=11.26$), Table S2). PD-PH reported riPH either to the side (n=14) or behind them (n=6), with no predominant location (Chi-square: p-value = 0.11, $\chi^2(1)=3.22$), while HC predominantly reported riPH behind them (n=14, and n=2 lateralized) (Chi-square: p-value = 0.006, $\chi^2(1)=9$). The most affected side did not influence the location of the riPH (all p-values>0.05). The very few instances in PD-nPH patients did not differ (behind: n=2; lateralized: n=1) (Chi-square: p-value = 1, $\chi^2(1)=0.33$). These data show that similarly to the sPH, PD-PH patients experienced riPH more often on the side, even if the tactile feedback was provided on the back, differing from HC, who always reported the location of the robot-induced presence behind them. Debriefing data also suggest that 38% of PD-PH patients report robotic-induced PH that are associated with a state that is

comparable in intensity to sPH. Interestingly, these robotic-induced sPH only occurred in the asynchronous stimulation condition.

Supplementary S8

sPH in PD-PH (semi-structured interview data).

Previous studies observed that most patients with PD who experience PH report them as neutral, as not distressing (except when it occurred for the first time), and usually short-lasting. Moreover, PH are typically felt beside or behind the patient's body (rarely also in an adjacent room)(11). In the current study, the semi-structured interview data confirmed that sPH in PD-PH patients were in 54% neutral or positive and were in 62% of undetermined gender. In 69% the presence was either felt on the side of the patient's body and/or on the back (for other variables see Table S2). Collectively, these results are compatible with previously reported sPH in PD. Overall sPH were not predominantly located in one spatial position. That is, ~38% of the patients experienced the sPH on either sides (not simultaneously) and/or in the back, confirming that sPH are not associated with the predominantly affected side of the disease (11) (Table S4 for details). None of the patients reported hallucinations within the hour after the robotic stimulation (while still in the laboratory).

	Number of patients	**%**
PH Valence		
• Positive/Neutral	7	54
• Negative	6	46
PH Gender		
• Female only	2	15
• Male only	1	8
• Both sex	2	15
• Undetermined	8	62
PH Lateralisation		
• Side only	6	46
• Back only	3	23
• Back and Side	2	15
• Front	1	8

• Other room	5	38
Occurrence (moment)		
• Day	3	23
• Night	4	31
• Anytime	6	46
Occurrence (place)		
• Home only	8	62
• Outside home only	0	0
• Both	6	46
Distance of PH		
• Less than 1m	5	38
• More than 1m	8	62

Table S4. Phenomenology of the symptomatic PH in PD.

Study 1.2: riPH in PD-PH patients depend on sensorimotor delay

Supplementary S9

Participants

The same participants of study1.1 took part in study1.2. In total, 10 PD-PH and 12 PD-nPH and 21 HC participated to study1.2. Because of fatigue and/or tremor, two PD-PH and one PD-nPH could not participate in study1.2. One PD-PH and one PD-nPH were excluded from the analysis because they performed less than 18 trials (i.e. one session) before definitively interrupting the experiment, due to fatigue and/or excessive tremor.

Supplementary S10

Experimental procedure

For each patient, the task of study1.2 was done exclusively with the hand that was most affected by PD. HC did the task with their dominant hand. Each participant was asked to perform three sessions; each session consisted of 18 trials (3 repetitions per delay). In total, each delay was repeated 9 times. The overall experiment lasted approximately 20 minutes. Between each session, the participant could take a break according to his/her needs. One PD-PH patient performed longer sessions. In total, PD-PH completed 57.8 ± 16.9 (mean ± SD) trials, PD-nPH completed 45 ± 12.8 (mean ± SD) trials, and HC completed 53.3 ± 3.91 (mean ± SD) trials. No statistically difference across groups was observed (Welch two Sample t-test,

two-tailed): PD-PH vs. PD-nPH: t(17) = 1.97, p-value = 0.065; PD-PH vs. HC: t(-9) = 0.89, p-value = 0.39.

Supplementary S11

Degree of sensorimotor conflict modulates riPH

Study1.2 confirmed that PD-PH patients experienced stronger riPH than PD-nPH patients (main effect of group: permutation p-value = 0.016; Fig.1D). Comparing the intensity of riPH between PD-PH and HC, we observed that PD-PH patients have a stronger bias in experiencing riPH than HC (main effect of group: permutation p-value=0.046t), and that the intensity of riPH increased with increasing delays for both groups (main effect of delay: p-value<0.001, two-tailed permutation test; Fig. S1). Although PD-PH patients have a stronger bias in riPH, there was no significant difference in sensitivity (slope) between these two groups (p-value=0.6, two-tailed permutation test). On average PD-PH rated the riPH for the delays: 0ms: 35.1 ± 33.8 (percentage mean ± SD), 100ms: 34.8 ± 33.8, 200ms: 45.7 ± 38, 300ms: 39.8 ± 37, 400ms: 48.1 ± 39.5, 500ms: 48.4 ± 43.3. PD-nPH rated on average the riPH: 0ms: 6.75 ± 16.1, 100ms: 5.56 ± 19.2, 200ms: 8.33 ± 25.6, 300ms: 7.41 ± 22.4, 400ms: 8.33 ± 28.9, 500ms: 7.41 ± 25.7. HC rated on average the ri PH: 0ms: 14.3 ± 26.3, 100ms: 14.8 ± 28, 200ms: 15.3 ± 29.1, 300ms: 15.2 ± 28.3, 400ms: 23.8 ± 38.9, 500ms: 23.5 ± 34.9.

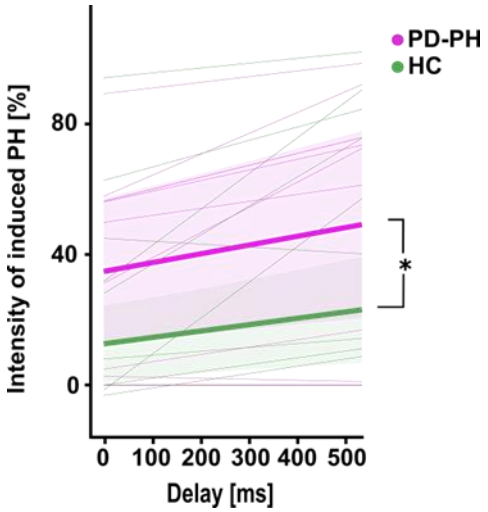

Figure S1. riPH (PD patient & HC). A. Study1.2. riPH were modulated by delay (permutation p-value<0.001) and PD-PH vs. HC had a stronger bias in experiencing riPH. The thicker lines indicate the mean of the fitted models, the thinner lines indicate the individual fit, and the shaded are indicates the 95% confidence interval.

Supplementary S12

Movement analysis

To assess whether the spatio-temporal pattern of the movement could explain the difference in rating of the riPH among groups, we calculated: i) the Inter-poke-interval (time between the end of the touch on the back of poke n and the beginning of the following touch – poke n+1), ii) duration of the poke and iii) the spatial distance between poke n and poke n+1. Data were analyzed with linear mixed effects models lme4 and lmerTest both R packages (12, 13). The significance of fixed effects was estimated with a permutation test (5000 iterations; predicted mean R package).

Inter-poke-interval (ipi). To assess the temporal aspects of the sensorimotor integration we computed the ipi for each individual and for each trial independently. Models were performed on the ipi for each subject, with Groups (i.e., PD-PH vs. PD-nPH; PD-PH vs. HC as fixed effects, and random intercepts for the participant.

Poke duration. To assess a second temporal aspects of the sensorimotor integration we computed the duration of each poke, for each individual and for each trial independently. Models were performed on the duration for each subject, with Groups (i.e., PD-PH vs. PD-nPH; PD-PH vs. HC) as fixed effects, and random intercepts for the participant.

Spatial distance between pokes. To further investigate the spatial aspects of the sensorimotor integration we computed the Euclidean distance between pokes for each trial and subject. Models were performed on each distance values for each subject, with Groups (i.e., PD-PH vs. PD-nPH and PD-PH vs. HC) as fixed effects, and random intercepts for the participant.

Supplementary S13

Movement analysis

Are bias and delay effect related to differences in the upper arm movements of PD-PH vs. PD-nPH patients during the robotic procedure? During Study1.2 we measured the movements performed by all participants, allowing us to analyze whether PD-PH, PD-nPH, and HC moved differently, calculating the inter-poke-interval (i.e., time between the end of the touch on the back (poke n) and the beginning of the following poke n+1) and the spatial distance between successive pokes (poke n and poke n+1).

The analysis of the movement data of Study1.2 exclude differences in movement patterns (neither temporal nor spatial aspects) between the two sub-groups of patients. No difference in the inter-poke-interval between PD-PH and PD-nPH (permutation p-value = 0.29). Average duration of the inter-poke-interval for PD-PH was 2.06±1.97 seconds (mean ± SD) and 1.55±2.26 sec for PD-nPH (mean ± SD). The duration of each poke did not differ between PD-PH and PD-nPH (permutation p-value=1). The average duration of the poke duration for PD-PH was 0.75±5.24 seconds (mean ± SD) and 0.73±2.82 seconds (mean ± SD) for PD-nPH (Fig.S2A-B). Spatial analysis of the movement revealed no difference in the distance between the pokes between PD-PH and PD-nPH (permutation p-value = 0.3). Average surface explication for PD-PH was 17.83±18.4 mm (mean ± SD) and 23.89±21.05 mm for PD-nPH (mean ± SD) PD-PH were not significantly slower in performing poking movement than HC (1.57±2.08; mean ± SD) (permutation p-value=0.097). The duration of each poke did not differ between PD-PH and HC (permutation p-value=0.076), the average duration of the poke duration for HC was 0.49±0.39 seconds (mean ± SD). No differences were observed in the spatial aspects of the movement between PD-PH and HC (permutation p-value = 0.067). The average surface explored for HC was 29.45±25.78 mm (mean ± SD).

These movement data show that both PD groups and the elderly HC were well able to carry out sensorimotor stimulation during the robotic procedure and, importantly, that movement patterns did not differ between both patient groups.

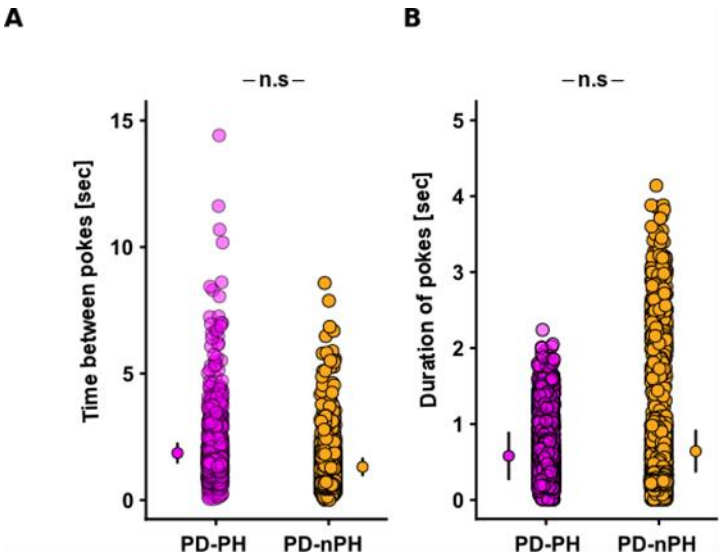

Figure S2. Analysis of the movement patterns during the sensorimotor stimulation. A. Mixed effects linear regression between the time between pokes for PD-PH (purple) and PD-nPH (yellow). The duration did not differ significantly (permutation p-value=0.29) in the time between two pokes (inter-pokes-interval). B. Mixed effects linear regression between duration of the pokes. The duration of the pokes did not differ significantly (p-value=1). Error bar represent 95% confidence interval.

Supplementary S14

riPH are not due to clinical differences between PD-PH and PD-nPH

All patients were treated with anti-parkinsonian medications, but there was no significant difference in medication between both patient groups (Table S1). Although clinical experience and research has associated hallucinations with dopaminergic treatment (11, 14), the exact role between the dopaminergic system and hallucinations is currently debated (15, 16). Thus, PD patients can experience PH before starting any dopaminergic medication (17) and the use of levodopa and dopamine agonists was not found to modulate occurrence of PH (15). Motor fluctuations have also been linked to PH (18) (for a review (15)) and it is known that PH and other hallucinations occur more frequently in advanced stages of PD (16). Thus, the difference in riPH between the two PD groups was not related to differences in disease duration, motor impairment, motor complications, or to dopaminergic treatment or hyperdopaminergic behavior (no significant differences between PD-PH and PD-nPH: all p-values>0.05; two-tailed permutation test; Table S1-2). Analyzing several other clinical and demographic variables (including motor impairment, dopaminergic treatment, and) that have been associated with symptomatic hallucinations in PD (e.g. (18)). We found no evidence for a difference between the two sub-groups of patients (all p-values>0.05; Table S1 for demographic of sub-groups).

Between the two sub-groups of patients with PD, there were no statistically significant differences (p-values>0.05) in the performance on the Montreal Cognitive Assessment (MoCA), disease duration, dopaminergic treatments (levodopa daily equivalent dosage), apathy, hyperdopaminergic behavior (QUIP-RS), motor impairment (MDS-UPDRS-III) and motor complications (MDS-UPDRS-IV). Patients that felt the presence as a symptom of the disease, PD-PH (vs. PD-nPH), had a higher score on the score for risk of psychosis (PQ-16, part 1- assessing hallucinations, but not for part 2 - assessing the level of distress associated with the occurrence of hallucinations).

Collectively, these results suggest that the differences in robot induced-PH between PD-PH and PD-nPH cannot be explained by differences in the degree of neurodegeneration, dopaminergic treatment, or motor fluctuations (or any of the other clinical variables we measured).

It could be argued that our procedure may have induced a tactile hallucination. However, the following three reasons show that this is not the case. First, we investigated specific sensorimotor mechanisms, which involved proprioceptive, tactile and motor cues as well as additional robotically-controlled spatio-temporal cues related to the incongruency between these proprioceptive-tactile-motor signals. Our sensorimotor stimulation method employed tactile cues on the back in combination with distinct motor cues, with other distinct tactile cues, and with distinct proprioceptive cues (all three cues are related to movements of the upper limb performing the poking). Moreover, an important additional mechanism that we manipulate is the congruency of these different sensorimotor cues (in spatial and in temporal terms) via the front- and back-robot (see Figure 1A, Figure 2A), which resulted in robot-induced PH. Second, we note that tactile cues alone are not sufficient to induce riPH and that riPH are not mere tactile misperceptions or tactile hallucinations. If riPH were tactile misperceptions then every experimental condition (e.g. even the synchronous condition) should lead to PH, because they also contain tactile cues. However, this is not the case in Study 1 (experiment 1; Figure 1C) and was not the case in our previous work (9, 19). In addition, if PH would be a mere tactile “misperception”, it should also not be modulated by the degree of sensorimotor conflict (Study 1.2). Accordingly, our data on robot-induced PH do not reflect a tactile hallucination or tactile misperception. Rather, robot-induced PH are induced by the sensorimotor comparison between the different sensory signals (proprioceptive and tactile) and the motor signals. Finally, several PD-PH patients spontaneously indicated that riPH were comparable to their symptomatic PH, and a majority of PD-PH patients reported that they felt riPH to one side of their body (again similar to the symptomatic PH reported in PD generally and by the patients we tested) and thus at a location where no tactile feedback was provided.

More generally, tactile hallucinations and PH are distinct phenomena in phenomenological and neurobiological terms. Phenomenologically, sPH have not been described as tactile hallucinations and previous clinical research has shown that the felt presence is most often not only not seen or heard, but also not felt (i.e. 1, 3, 10, 11, 24).

Study 2

Study 2.1: riPH are associated with activation of a subcortical-cortical sensorimotor network in healthy subjects

Supplementary S15

Robotic system

The MR-compatible robotic system used to generate the sensorimotor conflicts was composed of a front and a back robot (Fig.2A in the main text; (20)). The front-robot of the MR-compatible robot contained a carbon-fiber rod attached to a slider allowing the participant to move along two directions (Fig.2A in the main text) and measured the movements. Movements of the carbon-fiber rod were electronically translated into movements of the back-robot. The back-robot was composed of a roller that touched the participant's back with stroking and tapping movements (for general performance of the robotic system see (20)). The back-robot's shape was adapted to the spatial dimensions of the scanner bore and a wooden mattress structure with a central slit was designed to allow the contact part of the back-robot to touch the back of the participants. The performance of the robotic system was previously validated inside a 3T and 7T MR scanner with a phantom (20). Visual Studio 2013 interface (Microsoft) was used to control the robotic system.

The robotic system used in this study differed from the one used in the study 1 and of Blanke and colleagues (9) in multiple aspects. First, the participants were in the supine position compared to the standing position. Secondly, due to the spatial constrains of the MR-environment, the movement of the participants were limited to the middle back and not the whole back and participants had less degree of freedom: they could only move in X (along the body) and Z (towards the body) directions. All these different aspects might have led to the decrease of intensity of the PH induction compared to the standing robot used in the previous study (9).

Supplementary S16

Mock scanner: pilot study

Here, we tested whether we could induce PH in supine position in a mock scanner using the MRI robot (i.e. riPH). All participants (n=24; 16 women, mean age±SD: 24.6±2.8 years old) had no history of neurological or psychiatric disorders. All participants were right handed as assessed by the Edinburg Handedness Inventory (21) (mean index: 81.0± 16.3 (SD) and range: 40-100). All participants provided written informed consent prior to the experiment. The study was approved by the Cantonal Ethics Committee of Geneva (Commission Cantonale d'Ethique de la Recherche-CCER). The Mock scanner (MRI Simulator, Psychology Software Tools, Inc.) mimicked the scanner environment as well as the noise of the echo-planar imaging sequence. Participants were asked to perform repetitive movements with their right hand and this operated the front-robot, the movements of which were translated to the back-robot that provided tactile feedback to our participants' backs. In two conditions, tactile feedback was delivered either synchronously with the participants' movements (synchronous control condition, sync) or with a delay (asynchronous condition, async) that was previously shown to induce the PH in healthy participants (Video S2). In a third condition (desynchronous condition, desync), movements of the back robot consisted of a pre-recorded sequence. Each condition lasted for 3 minutes, was repeated once, and given in random order. After each condition, a questionnaire adapted from (9) was filled where participants were asked to rate their degree of agreement or disagreement on a Likert scale from 0 to 6.

Supplementary S17

Mock Scanner (pilot study): Questionnaire results

All the ratings are summarized in Table S5.

Passivity experience ("I felt as if someone else was touching my body")

In line with prior work (22), we found that asynchronous robotic stimulations were associated with higher passivity experience than synchronous stimulation (main effect of Synchrony: permutation p-value < 0.001) with higher ratings in the async and desync conditions compared to the sync condition (post-hoc test: $t(46) = 2.16$, p-value = 0.035 and $t(46) = 4.75$, p-value < 0.001, respectively) and higher ratings in the desync compared to the async condition (post-hoc test: $t(46) = 2.59$, p-value = 0.012). These results further indicate a difference in the passivity experience between the desync and the async condition. This can be explained by the fact that the desync condition is a pre-recorded movement sequence

played on the back of the participants which is being completely decoupled with the participant's movement.

PH ("I felt as if a presence or someone was behind me")

A main effect of Synchrony was also found for PH (permutation p-value < 0.001) with higher ratings in the desync and async condition compared to the sync condition post-hoc test: ($t(46) = 4.14$, p-value < 0.001 and $t(46) = 2.92$, p-value = 0.00053, respectively). No significant difference between the async and desync ratings was found (post-hoc test: $t(46) = 1.13$, p-value = 0.26). Contrary to passivity experience, the desync condition did not elicit significantly higher ratings than the async condition suggesting that both condition generating sensorimotor conflicts can equally induce PH. Taken together, these results confirm previous findings in showing that passivity experience and PH are induced in the presence of strong sensorimotor conflicts, in line with the results found by Blanke and colleagues (9).

Self-touch ("I felt as if I was touching my body")

Regarding self-touch, only a trend for a main effect of Synchrony was found (permutation p-value=0.062), with a tendency for higher ratings in the sync condition compared to async and desync (Table S5 for ratings).

Question	Synchrony	Mean	Standard deviation
Self-touch	Desync	1.58	1.84
Self-touch	Async	2.08	2.10
Self-touch	Sync	2.54	2.48
I felt as if I was touching someone else's body	Desync	0.71	1.55
I felt as if I was touching someone else's body	Async	0.75	1.62
I felt as if I was touching someone else's body	Sync	0.50	1.29
Passivity experience	Desync	3.96	1.97
Passivity experience	Async	2.71	2.14
Passivity experience	Sync	1.67	1.97
PH	Desync	2.08	1.82
PH	Async	1.67	1.81
PH	Sync	0.67	1.55
Control (I felt as if I had no body)	Desync	0.67	1.09
Control (I felt as if I had no body)	Async	0.42	0.88
Control (I felt as if I had no body)	Sync	0.33	0.64
Control (I felt as if I had two right hands)	Desync	0.83	1.40
Control (I felt as if I had two right hands)	Async	0.75	1.51
Control (I felt as if I had two right hands)	Sync	0.63	1.06

Table S5. Mean ratings for all questions used in the mock scanner study

Movement analysis

To ensure that riPH were not due to any movement differences across experimental conditions, we calculated the total distance that each participant moved the front-robot. Analysis revealed no significant difference between the total distance covered in the synchronous versus asynchronous condition (permutation p-value = 0.96).

Supplementary S18

fMRI behavioral study 2.1: Questionnaire results

The questionnaire included only the first six questions of the mock scanner pilot study: "I felt as if I was touching my body", "I felt as if I was touching someone else's body", " I felt as if I had no body", "I felt as if I had two right hands", "I felt as if someone else was touching my body" and "I felt as if a presence or someone was behind me".

Passivity experience

Participants reported stronger passivity experiences in the asynchronous condition compared to the synchronous condition (main effect of Synchrony, permutation p-value < 0.001; Table S6).

Question	Synchrony	Mean	Standard deviation
Self-touch	Async	3.28	2.25
Self-touch	Sync	3.72	2.23
I felt as if I was touching someone else's body	Async	1.12	1.81
I felt as if I was touching someone else's body	Sync	0.88	1.59
Passivity experience	Async	3.40	2.25
Passivity experience	Sync	2.08	2.14
PH	Async	1.68	1.86
PH	Sync	1.04	1.65
Control (I felt as if I had no body)	Async	1.04	1.62

Control (I felt as if I had no body)	Sync	0.80	1.76
Control (I felt as if I had two right hands)	Async	0.56	1.33
Control (I felt as if I had two right hands)	Sync	0.36	0.76

Table S6. Mean ratings for all questions of the fMRI questionnaire

Supplementary S19

riPH-network in healthy subjects

We also analyzed fMRI data recorded in two control conditions that allowed us to control for two aspects of sensorimotor stimulation that are not related to PH and determined the brain regions that were commonly activated by either of the sensorimotor conditions (synchronous, asynchronous; Fig.S3A-B) vs. the control conditions (motor, touch; Fig.S3C-D). In the motor control condition, participants were asked to repeatedly move the front-robot with their right hand but did not receive any tactile feedback on their back (Fig.S3C). In the touch control condition, participants received touch feedback on their backs, but were not performing any movement with their right hand (the back-robot was actuated by a previously recorded movement sequence) (Fig.S3D).

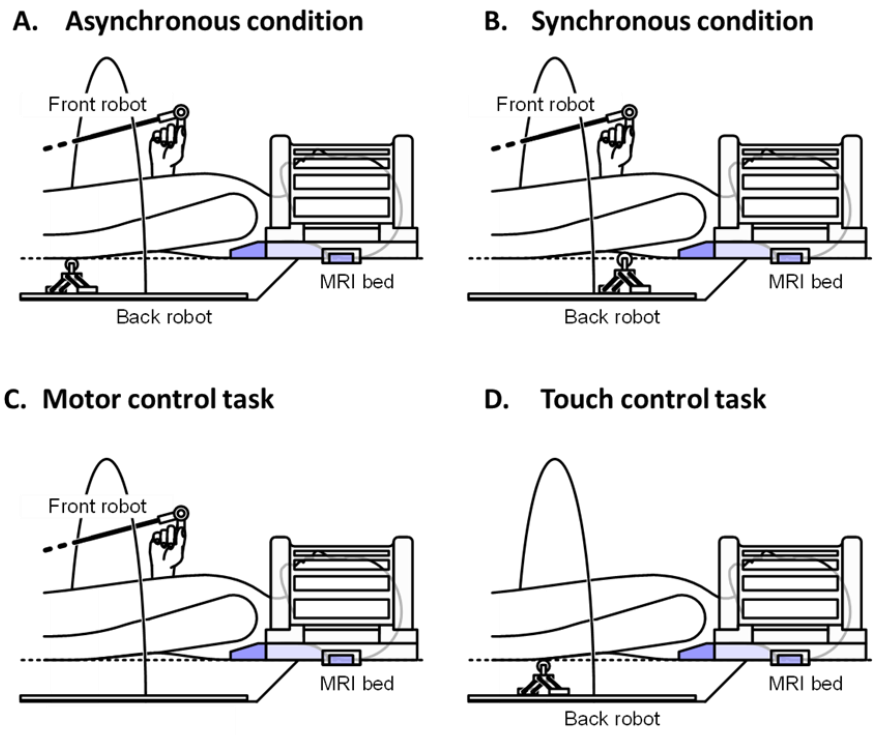

Figure S3. The different conditions assessed with MR-compatible robotic system. The MR robotic system consisted of two parts: a front robot composed by a carbon fibre rod with which the participants performed the movement in 2 directions (X and Z) and a back robot that reproduced the movement of the front robot in the back of the participants. Different conditions were tested: (A) an asynchronous condition where the back robot was delayed of 500 ms compared to the front robot, (B) a synchronous condition in which no delay was introduced between the front robot and the back robot. In addition, in the fMRI study, two conditions were added: a motor control task, in which the participant was just performing the movements without any tactile feedback on the back (C) and a touch control task in which the participant only received the tactile feedback on the back without any movement (D). The contact part is composed of a roller effector that enables to touch the back of the participant. Two ultrasonic motors (USR60-E3NT, Shinsei) enable the effector to move. A home-made mattress was designed with an aperture to allow robotic stroking on the participant's back, while lying down.

Supplementary S20

riPH are associated with activation of two sensorimotor networks in healthy subjects

Fig.S5B shows the activations when comparing the asynchronous condition with the motor plus touch control condition, revealing a large cortical-subcortical network including the left sensorimotor cortex (including adjacent parts of premotor cortex and superior parietal cortex), bilateral SMA and adjacent parts of cingulate cortex, bilateral putamen, the right ventral premotor cortex, the right inferior parietal cortex (IPL) and the right cerebellum (Table S8). Similar regions were found for the contrast between the synchronous and the motor plus touch control condition (Fig.S5A; Table S8). The synchronous versus asynchronous contrast did not show any significant brain activations. We also correlated riPH ratings or passivity experiences with brain regions activated more during the asynchronous condition compared to the synchronous condition and found no significant correlation (all p-values>0.05 after correcting for multiple comparisons). Activations from the conjunction analysis (Fig.2E main text) also did not correlate with PH ratings or passivity experiences (all p-values>0.05 after correcting for multiple comparisons).

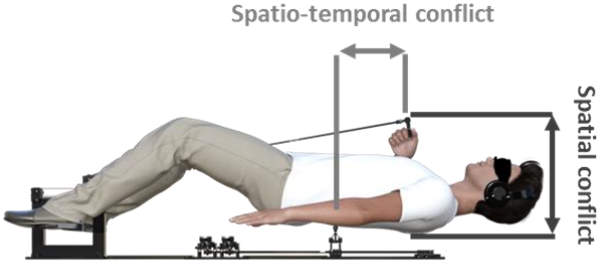

Figure S4. Sensorimotor conflicts present in the robotic experiment. In the synchronous and in the asynchronous condition, a spatial conflict is present between the hand movement and the touch delivered on the back of the participants (indicated in grey). In the delayed asynchronous condition an additional spatio-temporal conflict is present since the movement performed by the hand is delayed and then delivered to the back of the participants. (page 26 Supplemental information).

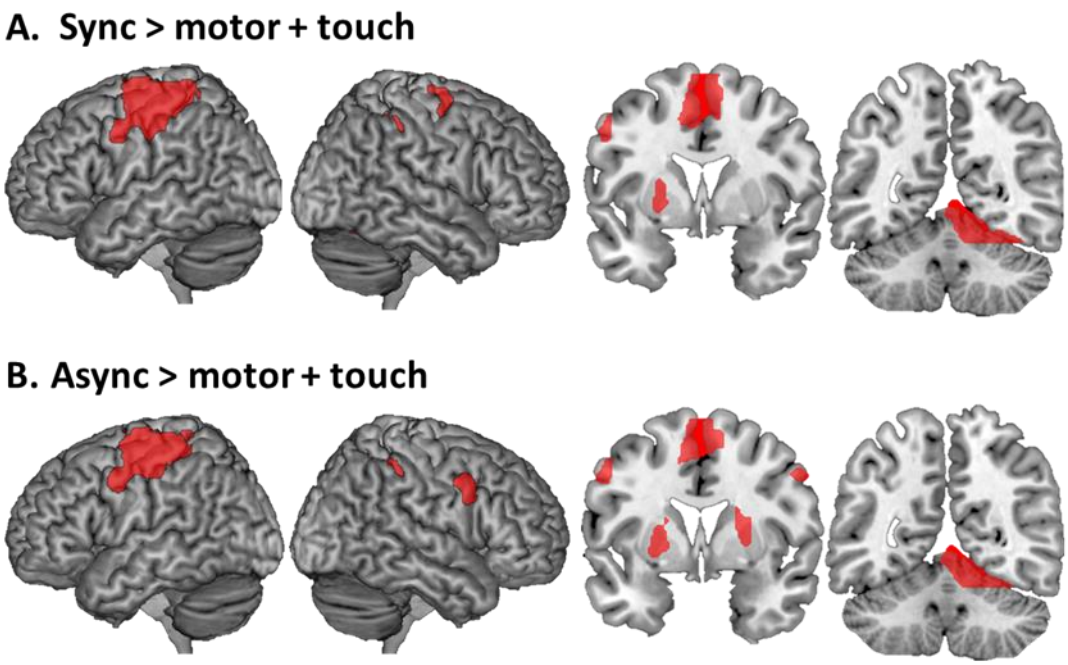

Figure S5. Robot-induced PH network. A. Brain regions responding to spatial sensorimotor conflict between the right-hand movement and the feedback on the back of the participants. **B.** Brain regions reflecting the spatio-temporal sensorimotor conflict.

Regions	Voxels	BA	MNI			Peak level	Cluster-level
			x	y	z	t value	*p* value FWE
R. medial prefrontal cortex (mPFC)	770	8/9/32	5	41	47	6.2	0.001
R. ventral premotor cortex (vPMC)/ Inferior Frontal Gyrus (Opercularis and triangularis) (IFG)	708	45/48	51	18	29	5.53	0.001
R. Anterior Insula (Ins)	566	47	36	24	-2	4.78	0.004
R. posterior Middle Temporal Gyrus (pMTG)	479	37	54	-54	0	4.99	0.01

Table S7. Spatio-temporal sensorimotor conflict PH regions. Regions activated during the contrast asynchronous > synchronous.

Regions	*Voxels*	*BA*	*MNI coordinates*			*Peak level*	*Cluster-level*
			x	*y*	*z*	*t value*	*p value FWE*
Asynchronous > motor + touch							
L. Sensorimotor cortex (primary motor cortex (M1), primary somatosensory cortex (SI), supplemental motor area (SMA), middle cingulate cortex (MCC), Superior parietal lobe (SPL))	9894	2/3/4/6/40	-26	-16	58	7.93	p<0.001
R. Cerebellum	2840		11	-58	-14	7.99	p<0.001
R. Putamen / Globus pallidum	599		22	3	8	6.33	p<0.01
L. Putamen / Globus pallidum	560		-22	1	5	6.07	p<0.01
R. Inferior parietal lobe/supramarginal gyrus (SMG)	503	2/40	41	-37	47	4.1	p<0.01
R. ventral premotor cortex	357	6	55	8	38	5.58	p<0.05
Synchronous > motor + touch							
L. Sensorimotor cortex (primary motor cortex (M1), primary somatosensory cortex (SI), supplemental motor area (SMA), middle cingulate cortex (MCC), Superior parietal lobe (SPL))	12843	2/3/4/6/40	-25	-18	57	8.85	p<0.001
R. Cerebellum	3057		12	-57	-14	8.17	p<0.001
R. Inferior parietal lobe/supramarginal gyrus (SMG)	600	2/40	40	-34	45	4.8	p<0.01
L. Putamen / Globus pallidum	449		-22	0	5	7.34	p<0.05
R. Superior frontal gyrus / dorsal premotor cortex	385	6	28	-8	65	4.62	p<0.05
Conjunction between the asynchronous > motor + touch and synchronous > motor + touch							
L. Sensorimotor cortex (primary motor cortex (M1), primary somatosensory cortex (SI), middle cingulate cortex (MCC), Superior parietal lobe (SPL))	12026	2/3/4/6/40	-26	-18	57	9.99	p<0.001
Supplemental motor area (SMA)		6	-5	-6	56	8.32	p<0.001
R. Cerebellum	2687		11	-57	-14	9	p<0.001
R. Inferior parietal lobe/supramarginal gyrus (SMG)	593	2/40	40	-34	45	4.59	p<0.01
L. Putamen / Globus pallidum	517		-23	0	4	6.44	p<0.01

Table S8. Robotically induced brain activations.

Study 2.2: Common PH-network for sPH and riPH

Supplementary S21

Lesion network mapping analysis

In order to assess the functional network derived from PH, we applied lesion network mapping (23). This method has the advantage of not requiring functional neuroimaging data from patients and of accounting for the possibility that symptoms may arise from remote brain regions connected to the lesioned brain region rather than the damaged area itself (24, 25). The PH-lesions reported by Blanke and colleagues (22) were used as seed ROIs except one lesion which was covering the whole brain, resulting in eleven lesions for the analysis. Briefly, the MR brain scans of the lesions were normalized to a smoothed T1 Montreal Neurological Institute space (MNI space) template and lesions were subsequently traced manually slice by slice on the normalised brain scan using MRIcron (https://www.nitrc.org/projects/mricron) (26). These lesion maps were then co-registered to the same MNI space than the healthy subjects from the Enhanced Nathan Kline Institute Rockland Sample.

All patients included in the analysis had PH (9). 1 of 12 patients with neurological lesions reported a tactile hallucination and this patient's tactile hallucination was not reported in relation to the PH.

fMRI acquisition

Resting state and T1-weighted structural data from 151 healthy participants obtained from the publicly available Enhanced Nathan Kline Institute Rockland Sample (27) was used. All participants were right-handed and aged between 19 to 40 years (25.8 ± 5.5 years, 83 females). Scans were acquired with a 3T Siemens Magneton TrioTim syngo. For the resting state data, a multiband EPI sequence was used (multiband factor = 4, 64 continuous slices, TR = 1.4 s, TE = 30 ms, flip angle = 65°, slice thickness = 2 mm) and 404 scans were collected. For each participant, an anatomical image was recorded using a T1-weighted MPRAGE sequence (TR = 1.9 s, TE = 2.52 ms, Inversion time = 900 ms, flip angle = 9°, 1 mm isotropic voxels, 176 slices per slab and FOV = 250 mm).

Data analysis

The pre-processing steps were performed using SPM12 toolbox (Wellcome Departement of Cognitive Neurology, Institute of Neurology, UCL, London, UK) in Matlab (R2016b, Mathworks). The first four functional scans were discarded from the analysis to allow for magnetic saturation effects: the analysis was performed on the 400 remaining scans. Slice timing correction and spatial realignment was applied to individual functional images. The anatomical image was then co-registered with the mean functional image and segmented into grey matter, white matter and cerebro-spinal fluid tissue. The functional and anatomical scans were then normalized to the MNI space. Finally, the functional scans were spatially smoothed with a 5 mm full-width at half-maximum isotropic Gaussian kernel.

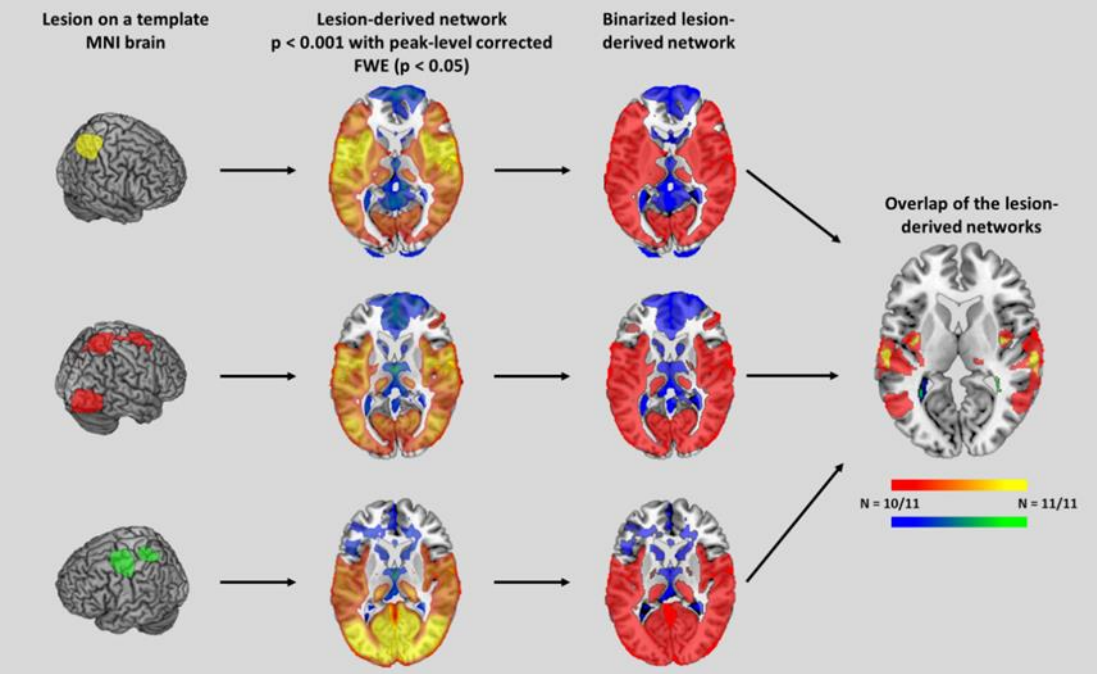

Figure S6. Lesion network mapping analysis. The steps of the lesion network mapping analysis are shown: first the lesion is mapped to a template brain, then this lesion is used as a seed ROI in a resting state functional analysis performed on a normative database. The network obtained for each lesion is thresholded at $p < 0.001$ with peak level corrected FWE ($p < 0.05$). All the lesions-derived networks are binarized and overlap to identify the regions functionally connected to most of the lesions.

Supplementary S22

Lesion network mapping: control analysis

To exclude that these regions are involved in hallucinations more generally, the same method was applied to a control group of eleven patients suffering from structured visual hallucination (VH) (28). The sPH-network was defined as those PH regions that were not overlapping with the visual hallucination derived network.

In addition, we determine whether the riPH-network was specifically connected to the lesions causing PH as opposed to the lesions causing VH. Therefore, for each of the 126 subjects in the database, the regionally-averaged resting-state BOLD signal time courses were extracted from each PH and VH lesion and riPH-network (Fig.2D-E in the main text) and were pairwise correlated (Fisher Z-transformed Pearson correlation) to establish the functional connectivity matrix. For each lesion location, we averaged the connectivity measures for the riPH-networks. Then, we compared statistically the connectivity between the two groups (PH vs. VH) using two sample t-test.

Supplementary S23

Results

Lesion network mapping control analysis

To exclude that these regions are involved in hallucinations more generally, the same method was applied to a control group of eleven patients suffering from structured visual hallucination (VH) (28), revealing a VH derived network consisting of mostly distinct regions (in bilateral TPJ, dorsal premotor cortex (dPMC), the left middle and superior occipital cortex, left thalamus and hippocampus (Table S11), as well as three common regions (bilateral posterior to middle STG and adjacent parts of parietal cortex; left PMC). Further analysis showed that the brain lesions causing sPH were more strongly connected with the riPH-network (as defined in healthy participants; study2.1) than the lesions causing visual hallucinations (difference between the two groups of lesions: t(18)=2.74, p-value=0.013, Fig.S7). A sPH-network was defined as those PH regions that were not overlapping with the visual hallucination derived network.

Regions	*Overlap*	*Hemisphere*	*Voxels*	*BA*	*MNI coordinates*		
					x	*y*	*z*
Positive correlation							
Superior temporal gyrus (STG)	11	Right	770	22	62	25	13
	11	Left	582	22	-58	-29	13
Insula	11	Right	124	48	37	-6	12
	11	Left	135	48	-37	-7	9
	11	Left	81	48	-35	-9	-8
Postcentral sulcus	11	Left	111	48	-58	-16	19
Middle cingulate cortex (MCC)	11	Right	53		9	-11	38
	11	Left	100		-9	-11	37
Inferior frontal operculum/ ventral premotor cortex (vPMC)	11	Right	86	45/48	42	17	23
Temporo-parietal junction (TPJ): STG, MTG (only right), supramarginal gyrus (SMG), rolandic operculum, vPMC	10	Right	7153	21/22/48	56	-18	18
	10	Left	5318	21/22/48	-52	-16	16
Fusiform area	10	Right	2842	19/37	37	-52	-16
	10	Left	2916	19/37	-36	-53	-15
Middle temporal gyrus (MTG)	10	Left	1292	37	-48	-62	11
Dorsal premotor cortex (dPMC)	10	Right	370	6	44	-5	53
	10	Left	308	6	-40	-8	51
Amygdala	10	Right	295	36	29	3	-24
	10	Left	112	36	-26	2	-26
Thalamus	10	Right	126		15	-25	2
	10	Left	120		-12	-27	-2
Cerebellum	10	Left	107		-10	-65	-46
Hippocampus	10	Rigth	70		23	-36	-2
	10	Left	90		-20	-37	-1
Putamen	10	Right	69		36	-10	-8
Cuneus	10	Right	68	18	17	-70	26
	10	Left	68	18	-14	-72	22
Suppplemental motor area (SMA)/Superior frontal gyrus	10	Left	58	6	-18	-8	68
Negative correlation							
Caudate	10	Right	70		17	-13	27

Table S9. Symptomatic PH-derived network. Brain areas that showed positive and negative correlation with most of the lesions (100% or 90% of overlap). Regions in the white matter were not reported.

Regions	*Overlap*	*Hemisphere*	*Voxels*	*BA*	*MNI coordinates*		
					x	*y*	*z*
Positive correlation							
Superior temporal cortex (TPJ)	10	Right	734	22/48	60	-14	9
	10	Left	148	42/22	-61	-32	14
	10	Left	147	22	-59	-9	-8
	10	Left	92	48	-51	-21	5
Middle and superior occipital cortex/ Inferior parietal lobule	10	Left	326	39/19	-38	-70	28
Hippocampus/parahippocampus	10	Left	118	20	-27	-31	-14
Thalamus/lingual area	10	Left	108	27	-14	-30	-2
Precentral cortex (dPMC)	10	Right	74	6	53	-3	44
	10	Left	51	6	-45	-7	51

Table S10. VH-derived network. Brain areas that showed positive correlation with 90 % of the VH lesion locations (only the regions in the grey matter are reported). There was no overlap for all the lesions.

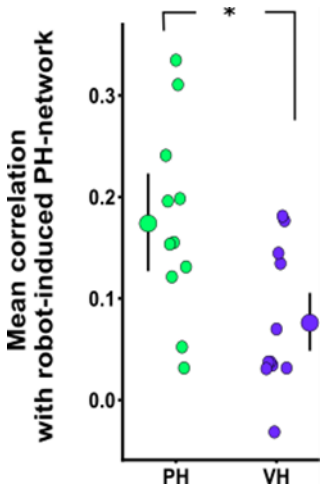

Figure S7. Lesion connectivity with the robot-induced PH-network. Lesions causing PH had greater functional connectivity with the riPH-network compared to VH lesions. * p-value<0.05.

Supplementary S24

Common PH-network

The common PH-network (cPH-network) was composed of regions overlapping between the sPH-network and the riPH-network and consisted in three anatomical regions in right IFG, right pMTG and two almost continuous PMC clusters (considered as one ROI for the following analysis).

Study 3

Study 3.1: Disrupted functional connectivity in cPH-network accounts for sPH in patients with Parkinson's disease

Supplementary S25

Participants

Data from thirty participants were analyzed in this study. All patients were prospectively recruited from a sample of outpatients regularly attending to the Movement Disorders Clinic at Hospital de la Santa Creu i Sant Pau (Barcelona) based on the fulfilling of MDS new criteria for PD with minor hallucinations (PD-PH) — sense of presence and/or passage hallucinations (n=15) — and without hallucinations (PD-nPH; n=15). Informed consent to participate in the study was obtained from all participants. The study was approved by the local ethics committee. The same dataset has been previously used in (29). Patients were diagnosed by a neurologist with expertise in movement disorders. Each patient was interviewed regarding years of formal education, disease onset, medication history, current medications, and dosage (levodopa daily dose). Motor status and stage of illness were assessed by the MDS-UPDRS-III(30). The PD-PH and PD-nPH groups did not differ for age, disease duration, dopaminergic doses, motor severity, cognition, depression, anxiety, and apathy (Table S11). All participants were on stable doses of dopaminergic drugs during the 4 weeks before inclusion. Patients were included if the hallucinations remained stable during the 3 months before inclusion in the study. No participant had used or was using antipsychotic medication.

	PD-PH (N = 15)	**PD-nPH (N = 15)**	***p-values***
Age	70.9 ± 1.5	65.9 ± 1.94	0.06
Gender	9 (M)	10 (M)	0.7 ($\chi 2$)
MoCA	25.3 ± 0.8	24 ± 1	0.3
PD-CRS	91.5 ± 4	94.2 ± 4.1	0.67
PD-CRS (frontal)	62.9 ± 3.8	65.7 ± 3.9	0.62
PD-CRS (posterior)	28.7 ± 0.4	28.5 ± 0.4	0.83
UPDRS III	21.7 ± 2.4	25.3 ± 2.03	0.2
LEDD (mg/day)	722.1 ± 73.8	581 ± 80.2	0.2
Dopamine agonists (mg/day)	151.3 ± 31.7	151.3 ± 31.7	0.9
Disease Duration (years)	5.3 ± 0.9	3.7 ± 0.6	0.2

Table S11. Clinical variables.

Exclusion criteria were history of major psychiatric disorders, cerebrovascular disease, conditions known to impair mental status other than PD, and the presence of factors that prevented MRI scanning (e.g. claustrophobia, MRI non-compatible prosthesis). Patients with focal abnormalities in MRI or non-compensated systemic diseases (e.g. diabetes, hypertension) were also excluded. In patients with motor fluctuations, cognition was examined during the "on" state. All participants were on stable doses of dopaminergic drugs during the 4 weeks before inclusion. Patients were included if the hallucinations remained stable during the 3 months before inclusion in the study. No participant had used or was using antipsychotic medication. All subjects had normal or corrected-to-normal vision. Informed consent to participate in the study was obtained from all participants. The study was approved by the local ethics committee.

Presence and type of minor hallucinations was assessed using the Hallucinations and Psychosis item of the MDS-UPDRS Part I. Participants with a sense of presence and/or passage hallucinations at least weekly during the last month were categorized as minor hallucinations. Cognitive functions were assessed by the Parkinson's Disease-Cognitive Rating Scale (PD-CRS) (31). Apathy was assessed with the Starkstein Apathy Scale (5).

We favoured the analysis of resting state fMRI over performing the robotic stimulation within the MRI, because for PD patients, performing long motor tasks (as required by the MRI to have a good signal to noise ratio) can be particularly tiring, and therefore exacerbating the tremor. Thus, the probability to have poor data quality and a high rate of patient willing to interrupt the experiment prematurely was too high.

Supplementary S26

Image acquisition & Image processing

MRI scans were acquired with a 3T Philips Achieva. T1 weighted scans were obtained using a Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence (TR = 500 ms, TE = 50 ms, flip angle = 8, field of view [FOV] = 23 cm with in-plane resolution of 256 × 256 and 1mm slice thickness). Resting-state functional MRI images were collected using an 8-minute sequence (TR = 2000 ms, TE = 30 ms, flip angle = 78, FOV = 240 mm, slice thickness = 3 mm).

Data analysis and standard pre-processing was performed using the functional connectivity toolbox CONN (https://www.nitrc.org/projects/conn/) and Statistical Parametrical Mapping (SPM 12) (http://www.fil. ion.ucl.ac.uk/spm/) for Matlab.

All functional MRI scans were normalized to the MNI space in order to be comparable. This transformation from native space to MNI space achieves better results when a co-registration between the functional scans and the T1-MRI scan is performed. Furthermore, the geometric transformation needed to warp the native T1-MRI scan to MNI space is applied to the functional scans, allowing to perform normalized voxelwise statistics.

Functional images were corrected for slice time and motion, co-registered with a high-resolution anatomical scan, normalised into Montreal Neurological Institute (MNI) space, resampled to 2 x 2 x 2 mm3, and smoothed with an 8 mm3 full width at half maximum (FWHM) Gaussian kernel for each subject. To estimate the excessive movement, the mean frame-wise displacement (FD) during the scanning was estimated with the exclusion threshold of 0.5 mm. The groups did not differ by the movement over the scanning period ($t = 1.18$, $p = 0.12$ with the mean FD of 0.29 ± 0.15 mm and 0.23 ± 0.16 mm for PD-PH and PD-nPH groups respectively) and did not reach the excessive movement threshold. Following the standard pipeline for confound removal of the CONN toolbox, the individual time courses of the segmented white matter and cerebrospinal fluid, the 6 motion parameters with rigid body transformations and their first-order derivatives, and global signal time courses were extracted and regressed out of the data. Regressions were performed for the entire time-series. The blood oxygenation level dependent (BOLD) signal data were passed through a band filter of 0.01-0.1 Hz. A whole-brain grey matter mask in MNI space restricted data analysis.

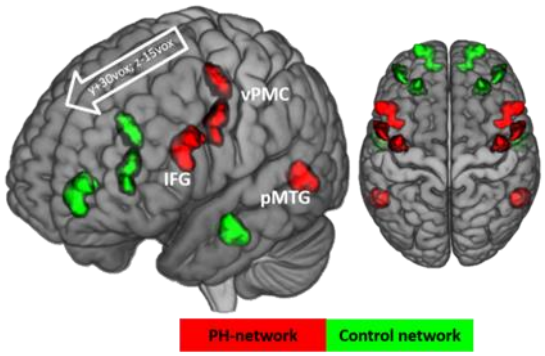

Figure S8. Control regions for the resting state fMRI analysis of PD patients. Bilateral PH-network areas (red) shifted forward (green): Inferior frontal gyrus (IFG) x±20 y+30 z-15; ventral premotor cortex (vPMC) x±10 y+30 z-15; posterior middle temporal gyrus (pMTG) x y+30 z-15

Connections	Variable Importance
Left-IFG - Left pMTG	1
Left pMTG - Right vPMC	0.913
Left IFGlh - Right vPMC	0.797
Left pMTG - Right pMTG	0.710
Left IFG - Right pMTG	0.652
Left IFGlh - Left vPMC	0.348
Right IFG - Right vPMC	0.333
Right pMTG - Right vPMC	0.333
Left pMTG - Left vPMC	0.319
Right IFG - Right pMTG	0.225
Right pMTG - Left vPMClh	0.203
Left vPMC - Right vPMC	0.188
Left IFG - Right IFG	0.174
Right IFG - Left vPMC	0.123
Right IFG - Left pMTG	0

Table S12. Contribution of each connectivity to the classification of PD-PH, values scaled between zero and one. Each variable's importance is calculated based on the absolute value of the t-statistic for each model parameter used (32). To facilitate the interpretation and comparison with other models the values are normalized between 0 and 100.

Supplementary References

1. Z. S. Nasreddine, N. A. Phillips, V. Bédirian, S. Charbonneau, V. Whitehead, I. Collin, J. L. Cummings, H. Chertkow, The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 53, 695–699 (2005).

2. N. Carson, L. Leach, K. J. Murphy, A re-examination of Montreal Cognitive Assessment (MoCA) cutoff scores. International Journal of Geriatric Psychiatry. 33, 379–388 (2018).

3. C. L. Tomlinson, R. Stowe, S. Patel, C. Rick, R. Gray, C. E. Clarke, Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Movement Disorders. 25, 2649–2653 (2010).

4. D. Weintraub, E. Mamikonyan, K. Papay, J. A. Shea, S. X. Xie, A. Siderowf, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale. Mov. Disord. 27, 242–247 (2012).

5. S. E. Starkstein, H. S. Mayberg, T. J. Preziosi, P. Andrezejewski, R. Leiguarda, R. G. Robinson, Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 4, 134–139 (1992).

6. R. L. Loewy, C. E. Bearden, J. K. Johnson, A. Raine, T. D. Cannon, The prodromal questionnaire (PQ): preliminary validation of a self-report screening measure for prodromal and psychotic syndromes. Schizophr. Res. 77, 141–149 (2005).

7. I. de Chazeron, B. Pereira, I. Chereau-Boudet, G. Brousse, D. Misdrahi, G. Fénelon, A.-M. Tronche, R. Schwan, C. Lançon, A. Marques, B. Debilly, F. Durif, P. M. Llorca, Validation of a Psycho-Sensory hAllucinations Scale (PSAS) in schizophrenia and Parkinson's disease. Schizophr. Res. 161, 269–276 (2015).

8. R. Cilia, C. Siri, M. Canesi, A. L. Zecchinelli, D. De Gaspari, F. Natuzzi, S. Tesei, N. Meucci, C. B. Mariani, G. Sacilotto, M. Zini, C. Ruffmann, G. Pezzoli, Dopamine dysregulation syndrome in Parkinson's disease: from clinical and neuropsychological characterisation to management and long-term outcome. J. Neurol. Neurosurg. Psychiatry. 85, 311–318 (2014).

9. O. Blanke, P. Pozeg, M. Hara, L. Heydrich, A. Serino, A. Yamamoto, T. Higuchi, R. Salomon, M. Seeck, T. Landis, S. Arzy, B. Herbelin, Report Neurological and Robot-Controlled Induction of an Apparition. Current Biology. 24, 2681–2686 (2014).

10. M. Hara, G. Rognini, N. Evans, O. Blanke, A. Yamamoto, H. Bleuler, T. Higuchi, in 2011 IEEE/RSJ International Conference on Intelligent Robots and Systems (2011), pp. 4664–4669.

11. G. Fénelon, T. Soulas, L. C. De Langavant, I. Trinkler, A.-C. Bachoud-Lévi, Feeling of presence in Parkinson's disease. J Neurol Neurosurg Psychiatry. 82, 1219–1224 (2011).

12. D. Bates, M. Mächler, B. Bolker, S. Walker, Fitting Linear Mixed-Effects Models Using lme4. Journal of Statistical Software. 67, 1–48 (2015).

13. A. Kuznetsova, P. B. Brockhoff, R. H. B. Christensen, lmerTest Package: Tests in Linear Mixed Effects Models. Journal of Statistical Software. 82, 1–26 (2017).

14. B. Ravina, K. Marder, H. H. Fernandez, J. H. Friedman, W. McDonald, D. Murphy, D. Aarsland, D. Babcock, J. Cummings, J. Endicott, S. Factor, W. Galpern, A. Lees, L. Marsh, M. Stacy, K. Gwinn-Hardy, V. Voon, C. Goetz, Diagnostic criteria for psychosis in Parkinson's disease: Report of an NINDS, NIMH Work Group. Movement Disorders. 22, 1061–1068 (2007).

15. A. Lenka, J. Pagonabarraga, P. K. Pal, H. Bejr-Kasem, J. Kulisvesky, Minor hallucinations in Parkinson disease: A subtle symptom with major clinical implications. Neurology (2019), doi:10.1212/WNL.0000000000007913.

16. D. H. Ffytche, B. Creese, M. Politis, K. R. Chaudhuri, D. Weintraub, C. Ballard, D. Aarsland, The psychosis spectrum in Parkinson disease. Nat Rev Neurol. 13, 81–95 (2017).

17. J. Pagonabarraga, S. Martinez-Horta, R. Fernández de Bobadilla, J. Pérez, R. Ribosa-Nogué, J. Marín, B. Pascual-Sedano, C. García, A. Gironell, J. Kulisevsky, Minor hallucinations occur in drug-naive Parkinson's disease patients, even from the premotor phase. Mov. Disord. 31, 45–52 (2016).

18. H. Kataoka, S. Ueno, Predictable Risk Factors for the Feeling of Presence in Patients with Parkinson's Disease. Mov Disord Clin Pract. 2, 407–412 (2015).

19. R. Salomon, P. Progin, A. Griffa, G. Rognini, K. Q. Do, P. Conus, S. Marchesotti, F. Bernasconi, P. Hagmann, A. Serino, O. Blanke, Sensorimotor Induction of Auditory Misattribution in Early Psychosis. Schizophr Bull (2020), doi:10.1093/schbul/sbz136.

20. M. Hara, R. Salomon, W. van der Zwaag, T. Kober, G. Rognini, H. Nabae, A. Yamamoto, O. Blanke, T. Higuchi, A novel manipulation method of human body ownership using an fMRI-compatible master-slave system. Journal of Neuroscience Methods. 235, 25–34 (2014).

21. R. C. Oldfield, The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia. 9, 97–113 (1971).

22. O. Blanke, P. Pozeg, M. Hara, L. Heydrich, A. Serino, A. Yamamoto, T. Higuchi, R. Salomon, M. Seeck, T. Landis, S. Arzy, B. Herbelin, H. Bleuler, G. Rognini, Neurological and Robot-Controlled Induction of an Apparition. Curbio. 24, 2681–2686 (2014).

23. A. D. Boes, S. Prasad, H. Liu, Q. Liu, A. Pascual-Leone, V. S. Caviness, M. D. Fox, Network localization of neurological symptoms from focal brain lesions. Brain. 138, 3061–3075 (2015).

24. A. D. Boes, S. Prasad, H. Liu, Q. Liu, A. Pascual-Leone, V. S. Caviness, M. D. Fox, Network localization of neurological symptoms from focal brain lesions. Brain. 138, 3061–3075 (2015).

25. M. D. Fox, Mapping Symptoms to Brain Networks with the Human Connectome. New England Journal of Medicine. 379, 2237–2245 (2018).

26. C. Rorden, M. Brett, Stereotaxic display of brain lesions. Behav Neurol. 12, 191–200 (2000).

27. K. B. Nooner, S. J. Colcombe, R. H. Tobe, M. Mennes, M. M. Benedict, A. L. Moreno, L. J. Panek, S. Brown, S. T. Zavitz, Q. Li, S. Sikka, D. Gutman, S. Bangaru, R. T. Schlachter, S. M. Kamiel, A. R. Anwar, C. M. Hinz, M. S. Kaplan, A. B. Rachlin, S. Adelsberg, B. Cheung, R. Khanuja, C. Yan, C. C. Craddock, V. Calhoun, W. Courtney, M. King, D. Wood, C. L. Cox, A. M. C. Kelly, A. Di Martino, E. Petkova, P. T. Reiss, N. Duan, D. Thomsen, B. Biswal, B. Coffey, M. J. Hoptman, D. C. Javitt, N. Pomara, J. J. Sidtis, H. S. Koplewicz, F. X. Castellanos, B. L. Leventhal, M. P. Milham, The NKI-Rockland Sample: A Model for Accelerating the Pace of Discovery Science in Psychiatry. Front Neurosci. 6 (2012), doi:10.3389/fnins.2012.00152.

28. L. Heydrich, O. Blanke, Distinct illusory own-body perceptions caused by damage to posterior insula and extrastriate cortex. Brain. 136, 790–803 (2013).

29. H. Bejr-Kasem, J. Pagonabarraga, S. Martínez-Horta, F. Sampedro, J. Marín-Lahoz, A. Horta-Barba, I. Aracil-Bolaños, J. Pérez-Pérez, M. Ángeles Botí, A. Campolongo, C. Izquierdo, B. Pascual-Sedano, B. Gómez-Ansón, J. Kulisevsky, Disruption of the default mode network and its intrinsic functional connectivity underlies minor hallucinations in Parkinson's disease. Mov. Disord. 34, 78–86 (2019).

30. Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. Mov. Disord. 18, 738–750 (2003).

31. J. Pagonabarraga, J. Kulisevsky, G. Llebaria, C. García-Sánchez, B. Pascual-Sedano, A. Gironell, Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. Mov. Disord. 23, 998–1005 (2008).

32. M. Kuhn, Astrophysics Source Code Library, in press.

5.3 THOUGHT CONSCIOUSNESS AND SOURCE MONITORING DEPEND ON ROBOTICALLY-CONTROLLED SENSORIMOTOR CONFLICTS AND ILLUSORY STATES

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Highlights

Thought insertion is an enigmatic and clinically-relevant conscious symptom in psychiatry. We report a new robotics-based approach to study though insertion experimentally.

We used robotic sensorimotor stimulation to induce the feeling of an alien presence, while participants performed source monitoring tasks.

Our results link thought insertion to source monitoring of self-related processing and specific sensorimotor processes.

Summary

Thought insertion (TI) is characterized by the experience that certain thoughts, occurring in one's mind, are not one's own, but the thoughts of somebody else and suggestive of a psychotic disorder. We report a robotics-based method able to investigate the behavioural and subjective mechanisms of TI in healthy participants. We used a robotic device to alter body perception by providing online sensorimotor stimulation, while participants performed cognitive tasks implying source monitoring of mental states attributed to either oneself or another person. Across several experiments, conflicting sensorimotor stimulation reduced the distinction between self- versus other-generated thoughts and was, moreover, associated with the experimentally generated feeling of being in the presence of an alien agent and subjective aspects of TI. Introducing a new robotics-based approach that enables the experimental study of the brain mechanisms of TI, these results link TI to predictable self-other shifts in source monitoring and specific sensorimotor processes.

Introduction

Thought insertion (TI) is one of the most enigmatic psychiatric symptoms and is characterized by the experience that certain thoughts, occurring in one's mind, are not one's own, but rather the thoughts of somebody else. TI violates basic intuitions about consciousness (i.e. Who else than me could possibly have access to my thoughts?) and has fascinated clinicians, scientists, philosophers, and laymen alike. TI is often reported by patients with schizophrenia and other psychotic disorders and are classified as so-called first-rank symptom, implying that a regular occurrence is suggestive of a psychotic disorder [1].

A long-standing question in psychiatric and cognitive neuroscience has been how the brain generates TI and on which brain mechanisms it depends. One prominent postulation is that first- rank symptoms, including TI, arise from a deficit comparable to those of conscious control for overt actions; that is, a deficit of source monitoring [2-4] and related sensorimotor mechanisms. This proposal is substantiated by converging behavioural, brain imaging, and electrophysiological evidence in patients with schizophrenia [4-6] and healthy subjects [7-10], but has so far targeted only conscious control of overt actions or auditory verbal hallucinations (i.e. alien voices [11]). Accordingly, the importance of source monitoring, self-related processes, and the link of TI to conscious monitoring of overt actions, remain poorly understood. Although some authors have investigated mechanisms related to TI using different cognitive manipulations [12,13] (see also [14-17]), research on TI and related cognitive processes has been hampered by the lack of empirical techniques in healthy subjects to probe TI and investigate associated behavioral changes in a more controlled fashion. Accordingly, the mechanisms of TI, and how they potentially depend on conscious control for overt actions and covert mental activity, remain unknown. In order to provide empirical evidence about the interaction between the sensorimotor control of actions and covert mental activity in potentially generating TI, here we applied a robotic device that allowed us to interfere in a specific and controlled way, with sensorimotor processing (known to alter source monitoring), while participants performed repetitive cognitive tasks.

Our recently developed robotic system consists of two robots and has previously allowed us to experimentally alter own body perception and, importantly, is able to induce illusory mental states mimicking psychosis-related symptoms, in a controlled manner in healthy

subjects [18]. During the procedure participants are asked to perform repeated poking movements, through a front robot (i.e. placed in front of participants) (Figure 1) and replicated by a back robot (i.e. placed behind the participants), resulting in controlled tactile stimulation on the participants' back based on their own movements (synchronous stimulation). Blanke et al. (2014) demonstrated that if a temporal delay is introduced between the participants' movements and the tactile stimulation delivered on their back (i.e. asynchronous sensorimotor stimulation) healthy participants experience an illusory alteration of their mental state characterized by passivity and loss of agency, as well as being in the presence of somebody else (feeling of an alien presence) (FoP).

In four separate experiments, we investigated whether thought-related source monitoring depends on (1) sensorimotor stimulation and on (2) the level of FoP while exposing our participants to asynchronous and synchronous (i.e. control condition) robotic stimulation. Importantly for the present experiments, previous work has shown that participants are able to carry out different covert cognitive paradigms while they are also actuating the robotic system and hence receive sensorimotor stimulation (i.e. [19-21]). In the present experiments, in Experiment 1, we tested the effects of robotic stimulation and FoP on source monitoring in a memory task by exploiting the so-called self-generation effect (SGE) and in Experiment 2 in a new task developed to assess thought numerosity (during a verbal fluency task). In Experiment 3, we investigated whether sensorimotor stimulation and the thought numerosity paradigm were associated with explicit changes in subjective thought experience. In a final control experiment, Experiment 4, we excluded that the observed effects were due to a generic reduction of attentional resources during asynchronous stimulation (by using a classical working memory task). Across these four experiments we demonstrate systematic behavioural and subjective changes in source monitoring suggestive of TI, while participants performed different mental operations, that depend on online conflicting sensorimotor stimulation and the level of experienced FoP. We discuss the importance of robotics and sensorimotor processes for the understanding of cognitive thought processes, including thought agency as well as abnormal and clinically relevant TI.

Results

Robotically-induced sensorimotor conflicts induce FoP and alter source monitoring

In Experiment 1, we used a robotic system [18,22] (Fig.S1) and exposed a group of healthy participants to repetitive sensorimotor stimulation that induces the FoP in a controlled way (see below), while they simultaneously performed a mental source monitoring task (Experiment 1). In this paradigm, inducing the so-called self-generation effect (SGE [23]; Supplementary Information), the participants were either presented with a list of words (passive condition) or they were asked to generate their own words (active condition) within a given set of rules. During an encoding phase, participants were asked to memorize both the self-generated and the passively heard words. When tested in a subsequent recognition phase, participants typically remember more self-generated than externally presented (heard) items, i.e. SGE. In order to avoid ceiling and floor effects in the recognition task for self-generated words, only the data of participants who generated more than 50% of expected associations (at least 18 words) and who performed above chance in the recognition task were included into analysis.

Importantly for the present investigation, our participants additionally performed repetitive movements to operate the front robot, which was combined with a second robot providing tactile feedback to their backs. In two conditions, tactile feedback was delivered either synchronously with their movement (synchronous control condition) or with a delay (of 500 ms; asynchronous condition) that, critically, we previously showed induces the FoP in healthy participants. In the first part of Experiment 1, while participants were using our robotic system, we asked them to carry out the standard procedure to measure the SGE. Previous work on the sense of agency for overt actions (and its link to self or source monitoring processes) has typically exposed subjects to different sensorimotor conditions, by varying the spatio-temporal contingencies between actions and associated sensory feedback or by measuring consequences in terms of sensory attenuation or motor adaptations [8-10,24-26]. As indicated above, the SGE is a well-known memory effect, characterized by better recognition for words that are self-generated (active condition) versus words that are only heard and generated by another person (passive condition [20]) (Fig.1A; Supplementary Information). Here, in order to study the relation between thought-related source monitoring and sensorimotor processing, we tested whether the magnitude of the SGE (i.e., the

difference between recognition for self-generated vs. generated-by-another words) was affected by the synchronous-asynchronous manipulation and the associated robotically-induced FoP.

Participants used the robotic system, either in the synchronous or asynchronous condition, during the word encoding session, i.e. while they were either generating or listening to words. The SGE for word recognition was tested immediately afterwards. We hypothesized that if asynchronous stimulation induces the FoP, it might also decrease source monitoring for self-generated concurrent mental operations, by decreasing a classical self-effect such as the SGE. As expected, we found a classical SGE (calculated as a recognition difference in d' between active and passive conditions), with significantly better recognition for actively (self) versus passively (other) generated words (Fig.1B) (self: M=4.12, SD=0.45; other: M=2.28, SD=0.65; $F(1,20)=180.86$, $p<0.0001$), confirming that participants better remembered words for which they have been the agents, as compared to words they passively heard. Critically, the SGE was modulated by the sensorimotor conditions (asynchronous versus synchronous) and this depended on the FoP strength (significant interaction between stimulation condition and FoP ratings used as a covariate; $F(1,20)=6.95$; $p=0.016$) (Fig.1C). In order to better illustrate how sensorimotor stimulation inducing the FoP effect differently affected recognition in the active and passive conditions, we divided the sample in two groups accordingly to their FoP ratings and directly compared the SGE between participants who did and who did not experience to be in the presence of an alien agent. There was a significant interaction between sensorimotor condition and FoP-group ($F(1,20)=7.217$, $p=0.014$): the SGE (i.e. difference between active and passive conditions) was lower in the FoP-inducing asynchronous (versus synchronous) condition, but only in participants experiencing the FoP (FoP group, synchronous: M=2.33, SD=0.75; asynchronous: M=1.53, SD=0.83)(Fig.1C). This was not the case in the other group of participants (No-FoP group, synchronous: M=1.43; SD=0.90; asynchronous: M=2.07, SD=1.04). In other words, when the robotically-applied sensorimotor conflict induced the experience to be in the presence of an alien agent (FoP), the SGE - an overt behavioural advantage in the ability to remember self- generated (active condition) versus other-generated words (passive condition) - was reduced. Importantly this effect was not due to a general interference on memory performance due to the robotic stimulation or to the induced FoP , as there was no main effect of sensorimotor stimulation ($p=0.58$) nor a stimulation X FoP interaction ($p=0.28$) on the performance in word recognition in general. This is an important

control, excluding that the found differences in the SGE depend on generic differences in distraction or divided attention between the two sensorimotor conditions.

To summarize, data from Experiment 1 show that the present sensorimotor conflicts induce selective behavioural changes in the SGE that tap into the brain's source monitoring processes (Fig.1C). Importantly, this SGE decrease in our participants' capacity to better remember self-generated versus other-generated words depends on the degree of feeling of an alien presence as induced by robotic stimulation (Fig.1D) and only in the conflicting asynchronous condition.

Perceived thought numerosity is associated with source monitoring and the feeling of an alien presence

Blanke et al (2014) demonstrated that the FoP, induced by the robotic stimulation in the asynchronous condition, was also associated with a change in how many people participants perceived to be close to them during sensorimotor stimulation (i.e. perceived social numerosity), such that participants perceived additional people to be present during the FoP-inducing asynchronous condition. Here we asked whether a similar change in numerosity judgements also occurs for the number of concurrent internal thoughts participants hold in their mind. This was also motivated because TI is not only characterized by the experience that certain thoughts, occurring in one's mind, are not one's own thoughts (loss of thought agency), but also by the sensation (or positive symptom) that the thoughts in one's mind are the thoughts of a different, alien and additional, person (i.e. TI proper [14, 15]). A lack of self-other discrimination or decrease in source monitoring as found in Experiment 1 is therefore not sufficient to account for TI that is also characterized by TI proper, because the former does not include a positive mental element characterized by the conscious attribution of one's thoughts to another additional agent. Moreover, the lack of thought agency without TI proper may also occur in healthy subjects, as is the case during unbidden thoughts [14,15,29], whereas TI proper has, to the best of our knowledge, not been reported in healthy subjects.

In Experiment 2 we investigated whether we can obtain a behavioural index for alienated thoughts similar to TI proper, that is an index for additional-inserted number of thoughts in healthy participants, and how this depends on the FoP. Blindfolded participants operated the same robotic system, while simultaneously performing a verbal (phonetic) fluency task [30]. With the aim to observe changes in overt behaviour that are associated with TI proper, we

adapted a verbal fluency task and asked a group of participants to estimate the number of words that they have either generated themselves (active condition) or listened to (passive condition), while operating the robotic sensorimotor system in either the synchronous or asynchronous condition. In the active condition, a starting phoneme was played to participants through headphones and they were instructed to generate as many words starting with the specified phoneme as they could in a given time period (phonetic fluency task), which randomly varied between 15-30s. Immediately afterwards, each participant estimated how many words he/she had generated. In the passive conditions, the participant listened to a list of words (of 6-10 words, randomized) (Fig.2A; Supplementary Information). To prevent participants from simply counting the words in the passive condition, and to avoid strong differences in cognitive load required between the two conditions, they were asked to determine whether each word they heard contained a given phoneme, specified at the beginning of each trial. In order to obtain a measure of how well subjects are able to estimate the number of "thoughts in their mind" (i.e. perceived thought numerosity), we subtracted the actual number of produced (active condition) or passively heard words (passive condition) from the estimated number of words. We predicted that sensorimotor stimulation should 1) differently impact perceived word numerosity, but specifically in the active self-generating condition (i.e. more thoughts as quantified through perceived word numerosity based on earlier elevated social numerosity judgements), and that 2) this should again (as in Experiment 1) be related to the strength of the robotically-induced FoP.

We found that participants underestimated the number of self-generated words (M=-0.90, SD=1.13) as compared to words generated by another agent (M=0.55, SD=1.11; main effect active-passive: $F(1,18)=23.306$, $p<0.0001$). Critically, this self-suppression effect depended on sensorimotor stimulation (active-passive by sensorimotor condition interaction: $F(1,18)=7.274$, $p=0.015$), as the number of estimated words in the active conditions differed in the asynchronous (M=-0.75, SD=1.16) versus synchronous condition (M=-1.05, SD=1.17; $t(18)=2.192$, $p=0.042$). This was not observed when words were processed in the passive conditions (synchronous: M=0.69, SD=1.20; asynchronous: M=0.41, SD=1.14; $t(18)=1.668$, $p=0.113$) (Fig.2B), showing that these behavioural changes are not related to differences in attentional resources between the sensorimotor conditions or between the passive versus active condition.

We next tested whether this effect, that jointly depends on sensorimotor stimulation (asynchronous-synchronous difference) and source monitoring (active-passive difference), is also associated with the FoP. This was confirmed by the finding that the asynchronous-synchronous difference for the numerosity judgment of actively generated words correlated positively with the FoP intensity (rho=0.41, p=0.04) (Fig.2C). That is, the stronger a participant experienced the FoP, the more her self-suppression effect in thought numerosity judgments was reduced in the asynchronous (as compared to the synchronous) condition, that is perceived numerosity of self- generated words became more similar to other-generated words.

Additional analyses excluded that these effects were due to generic differences in attentional resources or cognitive load between experimental conditions. There was no difference in the total number of generated words in the active condition (M=7.95, SD=2.02) and the number of words where the correct phoneme was identified in the passive condition (M=8.11, SD=0.33; F(1,18)=0.115, p=0.738), or between both sensorimotor conditions (synchronous: M=8.18, SD=1.18; asynchronous: M=7.88, SD=0.89; F(1,18)=3.079, p=0.096), nor there was an interaction between the source (active – passive) and sensorimotor stimulation (F(1,18)=0.944, p=0.344). These effects were also not modulated by the experienced FoP, as when FoP ratings were as a covariate, no main effects nor interactions emerged (all p-values>.35; see also Supplementary Results).

To summarize, these data reveal a robotically-induced reduction of thought-related source monitoring characterized by a reduced ability to discriminate mental processes representing self- generated thoughts from those generated by others, making thought numerosity judgments more similar for words that were either actively generated or passively heard, independently of differences in cognitive load between the present experimental conditions. Importantly, the direction of the self-suppression effect suggests that perceived thought numerosity in the asynchronous active condition (as compared to the synchronous active condition) is shifted towards performance in the passive conditions, i.e. in conditions during which participants judge items generated by another person. This was further corroborated by linking this shift in performance to the experimental induction of being in the presence of an alien agent (FoP), because self-generated words were perceived as more similar to other-

generated words in the FoP-inducing asynchronous condition and because the self-suppression effect correlated positively with FoP intensity. Accordingly, the number of self-generated words were perceived as higher and more similar to the number of other-generated words, selectively in the FoP-inducing asynchronous condition, suggesting that under these conditions additional and alien-like thoughts were inserted into the minds of our participants (TI proper), compatible with previous findings on the perceived number of alien people (social numerosity [18]).

Subjective mental state related to TI depends on the feeling of an alien presence and sensorimotor stimulation

We finally sought to provide additional evidence whether the experimental conditions leading to the changes in overt behaviour in Experiment 2 are associated with changes in subjective TI and whether this depends on processes of source monitoring and the FoP. To this aim in Experiment 3, we asked a new group of participants to perform the verbal fluency task (active condition as in Experiment 2), while operating the robotic system in either the synchronous or asynchronous condition (see Methods). At the beginning of each condition, they heard a French phoneme through headphones, and were then asked to generate as many words as they could, starting with the specified phoneme within 3 minutes (phonetic fluency task [30]). At the end of each condition, they were asked to rate the items on a questionnaire referring to their thought process during the task (Fig.3A). The questionnaire was based on previous TI literature [31,32] and contained a total of twelve items, with six items assessing TI and other aspects of thought consciousness, as well as six control items (Tab.S2). Both sensorimotor conditions were then repeated in randomized order (without the verbal fluency task) followed by the FoP questionnaire as used in the previous experiments (Supplementary Information). We predicted that experimental TI and related aspects of thought consciousness would be stronger during asynchronous versus synchronous sensorimotor stimulation and that it would be associated with the experience of an alien presence (FoP).

Accordingly, results showed that that sensorimotor stimulation affected thought-related items, but not control items, and that this effect depended on the FoP strength as induced by the asynchronous stimulation. Indeed, there was a significant interaction between the type of question (thoughts experience, control), sensorimotor stimulation (synchronous, asynchronous), and FoP score ($F(1,17)=7.49$, $p=0.011$, $\eta 2=0.30$). Further analysis, run on

thought experience questions only, showed a marginally significant stimulation X FoP interaction ($F(1,14)=4.32$, $p=0.05$; $\eta2=0.19$), suggesting that the sensorimotor stimulation conditions differently affected subjects responses, as a function of whether they did or did not perceive the FoP. When analyzing individual questions, the sensorimotor X Question (Q1, Q3, Q7, Q8, Q10 and Q11) X FoP interaction was significant ($F(5,85)=4.60$, $p<0.001$; $\eta2=0.19$), indicating that the effect of sensorimotor stimulation was stronger for some key experimental questions assessing different aspects of thoughts experience. Question-by-question analysis then revealed that, while performing the verbal fluency task, our participants reported mild experiences of thought insertion ("It seemed as if the robot put certain thoughts in my mind") and that their thoughts were manipulated ("It seemed as if the robot influenced some of my thoughts"). Importantly, as predicted, experimental TI and influence were stronger in the asynchronous as compared to the synchronous condition (thought influence; asynchronous: M=3.33, SD=1.64, synchronous: M=1.89, SD=1.49; Wilcoxon signed-rank test: Z=2.34, p=0.01) (TI; asynchronous: M=2.00, SD=1.41, synchronous: M=1.61, SD=1.38; Wilcoxon signed-rank test: Z=2.11,p=0.03; asynchronous: M=2.5, SD=1.71, synchronous: M=1.67, SD=1.15; Wilcoxon signed-rank test: Z=- 1.91, p=0.03) (Fig.3B; Tab.S2). As expected18, participants also gave higher ratings for the FoP in the asynchronous (M=3.95; SD=2.07) versus synchronous condition (M=2.56; SD=2.06) (Wilcoxon signed-rank test: Z=-2.69, p=0.005) and for passivity experiences (asynchronous: M=4.5, SD=1.61; synchronous: M=2.77, SD=1.69; Wilcoxon signed-rank test: Z=-2.57, p=0.007; Supplementary Information). Further analysis revealed that the strength of thought insertion and thought influencing positively correlated with the intensity of the FoP (thought insertion: rho=0.56, p=0.01); thought influencing: rho=0.69, p=0.001) (Fig.3C). These selective effects were absent for control questions. We only observed a significant effect of question ($F(5,80)=5.41$, $p<0.001$, $\eta2=0.25$), showing that participants gave different ratings to the different items; however, these ratings did not differ as a function of sensorimotor stimulation and were not influenced by the FoP effect, as no other main effect nor interaction was significant (all p-values>.13). These results rule out a possible effect of suggestibility on the questionnaire items and further highlight the selectivity of the effects of sensorimotor stimulation and associated FoP on thought experience.

To summarize, the results from Experiment 3 demonstrate that repetitive spatio-temporal sensorimotor conflicts, while performing a verbal fluency task, induces sensations of thought alienation in healthy subjects. These sensations are weaker in intensity, but mimic aspects of

the phenomenology of TI and thought influence as reported by psychiatric patients with delusions. We again induced the FoP in the same (asynchronous) experimental condition and we, importantly, show that the stronger our participants felt to be in the presence of an alien agent (FoP), the stronger they felt that somebody else was thinking or influencing thoughts in their mind, showing that subjective and behavioural TI can be induced and modulated experimentally using sensorimotor stimulation during a repetitive verbal fluency task (Experiments 2,3).

Robotic-induced differences in thought-related source monitoring does not depend on differences in attentional demands

Results from Experiment 1 and Experiment 2 showed that the induced differences in self-monitoring during word memory and thought numerosity were specific for the asynchronous condition, were related to the experience of the alien agent (FoP), and did not manifest as a generic decrease in tasks performance; they were characterized by a specific reduction thought- related source monitoring (difference between active/self and passive/other processes). However, it could be argued that the higher level of sensorimotor incongruency in FoP-inducing asynchronous stimulation condition (compared to the synchronous condition) may have caused the described differences. Such an additional factor may have distracted participants, in turn more strongly affecting their SGE and thought numerosity judgments. To exclude this possibility, we tested the effects of robotic stimulation in the synchronous and asynchronous condition on a classic working memory 2-back task, well-known to require high-level attentional resources. If the effects of asynchronous stimulation depend on differences in attentional load between both conditions, then a reduction of working memory performance is expected specifically in the asynchronous condition. Conversely, the absence of a performance difference would rule out an attentional account, further corroborating our previous control analyses.

As expected, at the subjective level, questionnaires responses showed that participants reported higher scores in the questions assessing the FoP ("I felt as if someone was standing behind my body"), ($Z=20$, $p<0.03$, one-tailed; Wilcoxon) and passivity experiences ("I felt as if someone else was touching my body"; $Z=12$; $p<0.01$, one-tailed; Wilcoxon). However, the pattern of stimulation did not affect the performance in the working memory task, as there was no difference between conditions in task accuracy ($t(1,19)=0.26$, $p=0.54$; Cohen's $d=-0.14$;

synchronous condition, mean accuracy =92.1%; SD=5.4; asynchronous condition: mean=91.7; SD=5.8). Differently from the previous tasks aimed at measuring the effects of the robot on internal thought processes – i.e., the self-generation effect, Experiment 1 and the thoughts numerosity task, Experiment 2 -, the performance in the WM task was unrelated to the FoP effect. Indeed, when we added the FoP score (i.e., the asynchronous – synchronous difference in the FoP questionnaire) as a covariate, we did not find any difference in performance between conditions ($F(1,19)=1.83$, $p=0.19$, $\eta 2=0.86$), nor any interaction with the FoP score ($F(1,19)=0.63$, $p= 0.44$, $\eta 2 =0.29$). Thus, the robotic sensorimotor stimulation did induce a FoP in the asynchronous condition during a working memory task, but this did not alter participants' performance in such a demanding cognitive task. To provide further support to this conclusion, we also run Bayesian statistics allowing us to measure how confidently we can accept the null hypothesis of no difference between conditions. The Bayesian factor was 0.41 (error 0.0002), suggesting a moderate evidence for the null hypothesis. Data from Experiment 4, therefore, suggest that asynchronous sensorimotor stimulation and related FoP do no induce a generic reduction of attentional resources affecting cognitive performance in general, supporting the conclusions from Experiments 1-3 about a specific effect on source monitoring of one's own internal thoughts.

Discussion

Taken together, the behavioural data from Experiments 1-4 show that sensorimotor conflicts, applied during mental operations, reliably induce behavioural changes in thought-related source monitoring (SGE, perceived word numerosity), accompanied by alterations in thought consciousness that are compatible with some aspects of TI that are usually only seen in clinical populations. Importantly, these behavioural changes in conditions with increased TI are characterized by a reduced ability to discriminate mental processes representing self-generated thoughts from those generated by others, reducing the SGE for self-generated vs. other- generated words (Experiment 1) and making thought numerosity judgments more similar for words that were either actively generated or passively heard (and generated by another person) (Experiment 3). These effects were especially observed in individuals experiencing an alien presence that we induced by asynchronous sensorimotor stimulation, showing that our robotic manipulation of thought-related source monitoring is not just associated with the loss of thought agency and TI, but also with the feeling of the presence of an alien agent. Control analyses and the data from the control Experiment 4 further show that these effects cannot be explained by general differences in cognitive load between the two sensorimotor conditions. Accordingly, we argue that the present conflicting asynchronous sensorimotor stimulation in active, self- generating, conditions induces, in those participants experiencing the FoP, a mental state that is comparable to (albeit to a lesser degree and of short duration) to TI and thought alienation that is usually only reported by psychotic patients.

By defining a novel procedure that links robotics and cognitive science for the investigation of thought consciousness and its aberrations, the present approach offers, in healthy participants, novel insights into an enigmatic and clinically relevant psychotic symptom by firmly linking it to source monitoring and the FoP. Abnormal source monitoring has been shown to elegantly explain certain psychotic bodily experiences (i.e. somatic passivity [3]), has been proposed to account for other first-rank symptoms [2-4] (i.e. delusions of control; auditory verbal hallucinations), but had only limited success in explaining TI [3,33]. Importantly, previous research was not able to manipulate TI experimentally and especially not been able to induce TI-related mental states repeatedly and in controlled fashion (e.g., based on reaction time or accuracy measures) [12,13]. Central to our report is the experimental induction and manipulation of behavioural and subjective aspects of TI in

healthy subjects, providing implicit-behavioural (SGE; perceived word numerosity) and explicit-subjective (questionnaires) data that conflicting sensorimotor stimulation is sufficient to induce alterations in thought consciousness when participants perform active mental operations. Behaviorally, we demonstrate that the present robotically-induced TI is characterized by reduced source monitoring, a reduced ability to discriminate mental processes representing one's own mental operations from those representing mental operations of others, resembling passive thoughts and thoughts generated by another person, rather than one's own thoughts. Importantly, by manipulating specific sensorimotor processes that alter body representation [18], we show that these changes were especially prominent in individuals experiencing an illusory and experimentally-induced alien presence, as if the illusory alien presence (FoP) inserted alien thoughts into the mind of our healthy participants. We conclude that the present asynchronous sensorimotor stimulation induces in healthy participants, who tend to experience the illusory FoP, a mild and short-lasting behavioural and mental state that is reminiscent of symptomatic TI, so far reported only by psychotic patients.

Material and methods

Participants

A total of 93 healthy participants took part in four separate behavioural experiments. Experiment 1 consisted of 35 participants (11 female; mean age: M=20.5 years, SD=2.5 years), Experiment 2 of 19 participants (9 female; mean age: M=20.3 years, SD=2.4 years), and Experiment 3 of 19 participants (6 female; mean age M=20.9 years, SD=2.0 years), and Experiment 4 of 20 participants (10 female; mean age M = 28.4 years, SD = 6.29 years). All participants for Experiments were recruited by an advertisement at the EPFL campus (École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland) and at Campus Biotech (Geneva, Switzerland). All participants had normal touch perception and no psychiatric or neurologic history as assessed by self-report. All participants were native French speakers. Each participant only took part in one experiment only. All participants were naive to the purpose of the experiments and gave written informed consent to take part in the experiment. Experiments were approved by the EPFL ethics committee (Comité d'éthique de la recherche humaine) and were conducted according to the ethical standards laid down in the Declaration of Helsinki. Participants gave written informed consent after the experimental procedures were explained to them and were reimbursed for their participation with 20 Swiss Francs.

Apparatus

Robotic sensorimotor system. To experimentally create sensorimotor mismatch we adapted a bilateral master-slave robotic system that has been recently used to manipulate changes in bodily self-consciousness [18,21]. This system is composed of a commercial master haptic interface, the Phantom Omni (Sens Able Technologies), and a three degree-of-freedom slave robot. The slave device consists of two mechanisms: a belt-drive mechanism and a parallel-link mechanism. The belt-drive mechanism is made up of a belt linked to a direct-drive DC motor (RE 40, Maxon) moving a carrier on a linear guide allowing movements in the y (forward-backward) direction. The parallel-link mechanism is actuated through two harmonic drive motors (RH-8D 6006, Harmonic Drive Systems) and enables both tapping and stroking in x (right-left) and z (up-down) directions. These three motors equipped with optical encoders for positions sensing are connected to motor drivers (4-Q-DC Servoamplifier LSC 30/2 & ADS 50/5, Maxon) that receive the command voltages from a computer via PCI data acquisition cards (NI PCI-6221 & NI PCI-6014, National Instruments). The overall workspace of

the slave device is 200mm in the x direction, 250mm in the y direction, and 200mm in the z direction (See Figure S5). A load cell (ELPFTIM-50N, Measurement Specialties) is attached to the tip of the slave device in order to measure contact force. This allowed us to introduce a compliance factor on the system preventing the slave device from applying instantaneous strong force to the participants, making the interaction safer and more realistic. The system was controlled through an application programmed in Visual C++ (Microsoft) at a sampling rate of 1 kHz. The latency related to information transfer delays and computational processing necessary for mapping the master device movements to the slave device movements (i.e. touching the back of the participants) was equal to 1ms. The system had a bandwidth of approximately 2.5 Hz allowing a good synchrony between the master and the slave even during rapid and abrupt changes in velocity and direction [21]. This allowed reducing the constraints on participants' movements.

In each experiment, the participants were first explained the task and informed about the general procedure of the experiment. Then they were instructed on how to use the robotic device to apply touch on their back through the tip of the slave device. The experimenter demonstrated the type of movements they were supposed to perform during the experimental blocks. In particular, they were asked to perform tapping movements in front of them by holding the master device with both hands, while receiving the touch on their back by the slave device. They were allowed to tap in different directions (up-down, left-right) resulting in different touches applied on their back within a workspace of 200x200mm. In the training session, the participants used the system in the synchronous mode for about 1 minute without being blindfolded.

General experimental procedure

The robotic sensorimotor system was used to apply sensorimotor stimulation in the different experiments in two different conditions: synchronous sensorimotor stimulation (the participants were asked to move the lead robot via their right index finger, this way actuating the follow robot which provided immediate and congruent touches to the participant's back) and asynchronous sensorimotor stimulation (500 ms delay between the first robot operated via the right index finger and the second robot applying tactile feedback on the participants' back). During the robotic stimulation participants were always blindfolded. In each experiment, the participants were first explained the task and informed about the general

procedure of the experiment. Then they were instructed on how to use the robotic device to apply touch on their back through the tip of the follow device. The experimenter demonstrated the type of movements they were supposed to perform during the experimental blocks. In particular, they were asked to perform tapping movements in front of them by holding the lead device, while receiving the touch on their back by the follow device. They were allowed to tap in different directions (up-down, left-right) resulting in different touches applied on their back within a workspace of 200x200mm. In the training session, the participants used the system in the synchronous mode for about 1 minute without being blindfolded.

Experiment 1 – self generation effect: design, procedure and analyses

Experiment 1 was designed to assess the so-called self-generation effect (SGE [23]), originally described by Slamecka and Graf [5], while performing robotic stimulation. In this paradigm, the participants are either presented with a list of words (passive condition; participants only heard the words) or they were asked to generate their own words (active condition; participants produced and heard the words) within a given set of rules (see next two paragraphs for more detail). During the encoding session, we asked participants to memorize both the heard and the self-generated words. In the recognition session, participants were presented with a list of words (pre-recorded and played back), containing either the words they had generated or heard and other semantically related words, that were never presented and used as distractor (50% of target and 50% of distractor words were presented in random order). Participants were asked to determine for each word whether it is a word he or she had generated or heard during the encoding session or not. Participants typically remember the self-generated items (active condition) better than the heard items (passive condition). This phenomenon, termed self- generated effect, SGE, has been shown to be very robust and has been described in recognition and recall tasks and with a variety of materials, generation rules, and retention intervals [6].

Active condition. In the active conditions, participants heard 35 cue words, each followed by a cue letter. Participants were instructed to generate an associated word, which had to start with the specified letter, and utter it out loud. If the participant's generated word matched the predicted word (target word), the experimenter registered it, and the word was later used in the recognition task during the test recognition phase. The time interval between the cue

word and cue letter presentation was 1s, and participants' performance was self-paced in the encoding as well as in the recognition session.

Passive Condition. In the encoding session of the passive conditions, participants merely listened to 35 audio-played word pairs, and were instructed that they would be later tested for recognition of the second word in a pair [5].

Design and procedure. We performed a 2 x 2 factorial repeated measures design with the factor Sensorimotor stimulation (synchronous and asynchronous sensorimotor stimulation) and the factor Source (active, passive). Each participant therefore completed four experimental conditions, given in randomized order. At the beginning of each condition and before the encoding session started, we asked participants to move the robot for 60 seconds. During the encoding session, depending on the condition, they listened to either pairs of words (passive conditions) or they generated their own words after hearing a cue word and a cue letter (active conditions), while continuing to operate the robotic device. Participants wore headphones and were blindfolded throughout the encoding phase. After the encoding session, participants were asked to stop operating the robot and to remove the blindfolding and commenced the recognition task. At the end of the task and after each condition, participants were administered the questionnaire (see below).

Effect size estimation. We estimated the effect size for the self-effect for Experiment 1 based on the social numerosity task (study 4 in Blanke et al., 2014). Participants estimated to perceive on average 0.74 (SD=0.30) and 0.99 (SD=0.34) persons close to them, resulting in an effect size of 0.73 resulting on a suggested sample size of N = 28. We initially recruited 35 participants and we only included in the present analysis those participants, who produced enough word associations and whose performance was above chance (22). This sample size is in line with the original report of the Generation effect by [5] (N = 24).

Data analysis. In order to avoid ceiling effects in the recognition task for self-generated words, only the data of participants who generated more than 50% of expected associations (at least 18 words) were included into analysis. Also, participants who performed below chance level in the recognition task were excluded from analysis, leaving data from 22 remaining participants for further analysis. Task performance was defined by d-prime scores, which were

then analyzed with repeated measures ANOVA, with Source and Sensorimotor stimulation as the two within- subjects factors and the feeling of a presence (FoP) score as a covariate. Based on the recent finding that the FoP can be experimentally induced in healthy participants due to a specific spatial and temporal sensorimotor mismatch [4], we calculated the FoP score by subtracting the ratings of the FoP questionnaire item in the asynchronous from the ratings in the synchronous condition. Thus, higher FoP scores indicate a stronger FoP illusion due to the robotically induced sensorimotor mismatch.

Acquisition and preparation of auditory word stimuli. For Experiment 1, 250 word association pairs were first selected from the database of word association norms containing a collection of French words [7]. In order to balance the strength of association between the cue word and its associated target word across conditions, we have recruited 10 native French speakers (2 females; 18 – 23 years, M=20.1, SD=1.66). They were given the selected 250 cue words and cue letters (first letter of the predefined target word) to generate associations. The strength of the association was defined as the frequency with which participants chose the target word. 70 association pairs with higher association strength (0.7 - 1) were then selected for the self-generated conditions to increase the probability of participant generating the target word. 70 association pairs with lower association strength (0.3 - 0.6) were used for the other-generated conditions. Another 140 words were selected from the database to be used as distractor words during recognition task. The association pairs were then sorted into 4 alternative word lists (2 for self-generated and 2 for other-generated conditions), each consisting of 35 word pairs, with balanced association strength. Similarly, the distractor words were divided into 4 lists, each containing 35 distractor words. We verified, using the multivariate analysis of variance (MANOVA), that there was no significant difference in terms of frequency of use (www.lexique.org) and word length between the alternative lists ($F(6, 544)=0.494$, $p=0.813$) or between the target and distractor words ($F(2, 271)=0.001$, $p=0.999$). The word set was then recorded by two male and two female native French speakers and registered in wav format with 11025 Hz sampling frequency. In both Experiment 1 and Experiment 2, as well as during the pilot experiment (see below, Supplementary Results), the auditory word stimuli were played to participant in a gender-matched voice. In Experiment 1, two gender-matched voices were alternating between the encoding and testing phase in a balanced manner throughout the experiment.

Experiment 2 - Thought numerosity judgments: design, procedure and analyses

Experiment 2 was designed to estimate the number of thoughts in the participants' mind while performing robotic stimulation. To this aim, we implemented a fluency task, whereby, we asked participants to estimate the number of words that they have either generated themselves (active condition) or have listened to (passive condition), while operating the robotic sensorimotor system.

Design. We used a 2 x 2 factorial repeated-measures design, whereby we manipulated the Sensorimotor stimulation (synchronous and asynchronous sensorimotor stimulation) and the Source of the words to be estimated (active, passive). In the active conditions, a starting phoneme was played to participants through the headphones and they were instructed to generate as many words as possible starting with the specified phoneme, in a given time period (phonetic fluency task). This time period randomly varied between 15 and 30s, in order to avoid participants always producing and estimating a similar number of words. The experimenter counted and registered the words and, immediately afterwards, the participant had to estimate how many words she or he had generated. In the passive conditions the participants listened to a list of words, consisting of between 6 and 10 words (based on the number of words another group of participants generated in the active condition; see Pilot experiment in Supplementary Results). The number of words randomly varied throughout the trials. The words were played to participants with an inter-stimuli interval of 2.5s. All words and phoneme cues were presented to participants as auditory stimuli using MATLAB software (MathWorks, Inc.). In the passive condition, in order to prevent participants from counting the words, they were asked to determine whether each word they heard contains a phoneme, specified at the beginning of a trial. Each condition was repeated three times, and each repetition consisted of 4 trials, resulting in total of 12 numerosity judgments per condition. The order of repetitions of the different experimental conditions was counterbalanced across the participants. The dependent variable was the numerosity judgement accuracy, calculated by subtracting the actual number of played or produced words from the number of judged number of words. Prior to the beginning of the experimental session, participants went through a training session, comprising one repetition of each condition. Before or after the experiment in a counterbalanced manner, participants were asked to operate the robot for 60s in the synchronous and asynchronous mode (run in counterbalanced order), being

blindfolded and instructed to only focus on their movements and tactile feedback. After the synchronous and asynchronous blocks, they were given the FoP illusion questionnaire in order to measure the degree of the illusion induced by the sensorimotor stimulation.

Effect size estimation. Data from Experiment 1 were used to estimate the minimum sample size for Experiment 2 (self-effect part). In the group who experienced the FoP, the self-effect for asynchronous and synchronous stimulation was 1.53 (SD=0.83) and 2.33 (SD=0.75), resulting in an effect size of 1.008 and suggesting a minimum sample size of 15. We recruited 19 participants. For the questionnaire part, we estimated the required sample to replicate the FoP effect based on Study 3 from Blanke et al., 2014. The average ratings for the FoP question were 4 (SD=1.9) and 2.14 (SD=1.65) in the asynchronous and synchronous conditions respectively, resulting in a size effect of 1.30 and suggesting a sample size of 15 participants. We tested 19 participants via questionnaires assessing subjective thought insertion.

Data analysis. Two trials from two participants were discarded from analysis, because they failed to generate any word within the given time limit. The differences between the numerosity judgment and actual number of words (judgment accuracy) were averaged within each condition for each participant and then analyzed with repeated measures ANOVA where Sensorimotor stimulation (synchronous and asynchronous sensorimotor stimulation) and Source (active, passive) were used as within-subject factors.

Experiment 3 – changes in thoughts subjective experience: design, procedure and analyses

Experiment 3 was designed to measure whether robotic sensorimotor stimulation induced explicit changes in the subjective experience associated to internal thoughts. To this aim, a new group of participants again operated the robotic lead-follow system (as in Experiment 1 and 2), while simultaneously performing a phonetic fluency task. In a repeated-measures design, we manipulated the factor Sensorimotor stimulation (synchronous vs asynchronous). Participants manipulated the robotic system in synchronous and asynchronous mode for 3 minutes. At the start of each condition, they heard a French phoneme through headphones, and were then given three minutes to generate as many words as possible that started with the specified phoneme. At the end of each condition, they were asked to answer several questions referring to their thinking process during task performance (see below). The order of synchronous and asynchronous conditions was counterbalanced across the subjects.

Before or after the experiment in a counterbalanced manner, participants were also asked to operate the robot for 60s in both, synchronous and asynchronous modes while blindfolded and focused on their bodily sensations. After these synchronous and asynchronous blocks, they were given the FoP questionnaire (see below). In order to evaluate subjective experience during internal thoughts, we designed a detailed, 12 - item questionnaire. The items were constructed based on the literature on thought possession disorders [10,11] and particularly targeted feelings related to thought insertion (ex. “It seemed as if some outside force or person has put certain thoughts in my mind”), thought influence (ex. “It seemed as if some outside force or person has influenced some of my thoughts”), thought ownership (ex. “It seemed as if certain thoughts I had belonged to someone else”) and thought withdrawal (ex. “It seems as if some of my thoughts have been removed from my mind”). Other items, which served as control for suggestibility, pertained to positive psychotic symptoms, but not to disorders of thought possession, i.e. parasite thoughts, thought echoing, and voice distortion. The participants were asked to rate how much they agreed with each questionnaire item on a 7-point Likert scale (0 = not at all, 3 = not certain, 6 = very strong) (see Table 1B).

Experiment 4 - working memory task - design, procedure and analyses

Experiment 4 was designed to assess the effects of robotic stimulation on a working memory task. As in the previous experiments, blindfolded participants operated the robotic lead-follow system, while they were performing a 2-back verbal task, selected as a well-established paradigm and highly demanding in terms of cognitive resources. In a repeated-measures design, we manipulated Sensorimotor stimulation (synchronous vs asynchronous). Participants performed 16, 24 or 32 second blocks of sensorimotor stimulation with the robot either in the synchronous or asynchronous conditions, in counterbalanced order. During the stimulation, they were presented with a series of numbers (one every two seconds), which were administered via headphones. Subjects were required to respond (via button press) if the current number in the series was equal to the last but one heard in the series. Each condition consisted of 24 trials. At the end of the task, they were also presented with the BSC questionnaire assessing the FoP and related sensations (see below).

Effect size estimation. Effect size was calculated based on the results of Experiment 2. Given the obtained differences between self-generated and other-generated words and the associated standard deviations, resulting in a significant interaction between stimulation

condition and agent (p=0.015), the necessary sample size to replicate the effect with a p<0.05 is N=20.

Subjective changes in BSC

To measure changes in bodily self-consciousness as induced by the robotoc sensorimotor stimulation, for all experiments, we administered the same questionnaire as used previously (4).The questionnaire consists of 8 items, referring to the feeling of presence ("I felt as if someone was standing behind my body"), sensation of passivity ("I felt as if someone else was touching my body"), and other bodily illusions (see Supplementary Information). Two items served as control items for suggestibility (i.e. "I felt as if I had no body" and "I felt as if I had more than one body"). Participants were asked to designate on a 7-point Likert scale, how strongly they felt the sensation described by each item (0 = not at all, 3 = not certain, 6 = very strong).

Statistical Analysis. To assess statistical differences induced by the different experimental conditions on the subjective experiences (thoughts and BSC questionnaires), a one-tailed Wilcoxon signed rank test was applied to each question independently to compare response for the synchronous and asynchronous stimulation condition. One-tailed was decided because of the strong hypothesis that our effects would be always bigger for the asynchronous sensorimotor stimulation (4).

References

1 Schneider, K. Clinical psychopathology. (Grune & Stratton, 1959).

2 Feinberg, I. Efference copy and corollary discharge: implications for thinking and its disorders. Schizophrenia bulletin 4, 636 (1978).

3 Frith, C. D. The positive and negative symptoms of schizophrenia reflect impairments in the perception and initiation of action. Psychological medicine 17, 631-648 (1987).

4 Ford, J. M. & Mathalon, D. H. Electrophysiological evidence of corollary discharge dysfunction in schizophrenia during talking and thinking. Journal of psychiatric research 38, 37-46 (2004).

5 Shergill, S. S., Samson, G., Bays, P. M., Frith, C. D. & Wolpert, D. M. Evidence for sensory prediction deficits in schizophrenia. American Journal of Psychiatry 162, 2384- 2386 (2005).

6 Shergill, S. S., White T.P., Joyce D.W., Bays P.M., Wolpert D.M, Frith C.D. Functional magnetic resonance imaging of impaired sensory prediction in schizophrenia. JAMA psychiatry 71, 28-35 (2014).

7 Weiskrantz, L., Elliott, J. & Darlington, C. Preliminary observations on tickling oneself. (1971).

8 Shergill, S. S., Bays, P. M., Frith, C. D. & Wolpert, D. M. Two eyes for an eye: the neuroscience of force escalation. Science 301, 187-187 (2003).

9 Bays, P. M., Flanagan, J. R. & Wolpert, D. M. Attenuation of self-generated tactile sensations is predictive, not postdictive. PLoS biology 4, e28 (2006).

10 Bays, P. M., Wolpert, D. M. & Flanagan, J. R. Perception of the consequences of self- action is temporally tuned and event driven. Current Biology 15, 1125-1128 (2005).

11 Hoffman, R. E. Verbal hallucinations and language production processes in schizophrenia. Behavioral and Brain Sciences 9, 503-517 (1986).

12 Walsh, E., Oakley, D. A., Halligan, P. W., Mehta, M. A. & Deeley, Q. The functional anatomy and connectivity of thought insertion and alien control of movement. Cortex 64, 380-393 (2015).

13 Sugimori, E., Asai, T. & Tanno, Y. Sense of agency over thought: external misattribution of thought in a memory task and proneness to auditory hallucination. Consciousness and cognition 20, 688-695 (2011).

14 Stephens, G. L. & Graham, G. When self-consciousness breaks: Alien voices and inserted thoughts. The MIT press (2000).

15 Martin, J.-R. & Pacherie, E. Out of nowhere: thought insertion, ownership and context-integration. Consciousness and Cognition 22, 111-122 (2013).

16 Gallagher, S. Neurocognitive models of schizophrenia: a neurophenomenological critique. Psychopathology 37, 8-19 (2004).

17 Vicente, A. The comparator account on thought insertion, alien voices and inner speech: some open questions. Phenomenology and the Cognitive Sciences 13, 335-353 (2014).

18 Blanke, O. Pozeg P., Hara M., Heydrich L., Serino A., Yamamoto A., Higuchi T., Salomon R., Seeck M., Landis T., Arzy S., Herbelin B., Bleuler H., Rognini G. Neurological and robot-controlled induction of an apparition. Current Biology 24, 2681-2686 (2014).

19 Salomon R, Progin P, Griffa A, Rognini G, Do KQ, Conus P, Marchesotti S, Bernasconi F, Hagmann P, Serino A, Blanke O. Sensorimotor Induction of Auditory Misattribution in Early Psychosis. Schizophr Bull. 8;46(4):947-954 (2020).
20 Faivre N, Vuillaume L, Bernasconi F, Salomon R, Blanke O, Cleeremans A. Sensorimotor conflicts alter metacognitive and action monitoring. Cortex. 124:224-234 (2020).
21 Orepic P., Rognini G., Kannape O.A., Faivre N., Blanke O. Sensorimotor conflicts induce somatic passivity and louden quiet voices in healthy listeners.
BioRxiv (2020).
22 Hara, M. Rognini G., Evans N., Blanke O., Yamamoto A., Bleuler H., Higuchi T. A Novel Approach to the Manipulation of Body-Parts Ownership Using a Bilateral Master-Slave System. IEEE/RSJ International Conference on Intelligent Robots and Systems, pp. 4664-4669 (2011).
23 Slamecka, N. J. & Graf, P. The generation effect: delineation of a phenomenon. Journal of experimental Psychology: Human learning and Memory 4, 592 (1978).
24 Blakemore, S.-J., Wolpert, D. & Frith, C. Why can't you tickle yourself? Neuroreport 11, R11-R16 (2000).
25 Blakemore, S. J., Wolpert, D. M. & Frith, C. D. Central cancellation of self-produced tickle sensation. Nature neuroscience 1, 635-640 (1998).
26 Wolpert, D. M. & Ghahramani, Z. Computational principles of movement neuroscience. nature neuroscience 3, 1212-1217 (2000).
27 Koehler, K. First rank symptoms of schizophrenia: questions concerning clinical boundaries. The British Journal of Psychiatry 134, 236-248 (1979).
28 Taylor, M. A. Schneiderian first-rank symptoms and clinical prognostic features in schizophrenia. Archives of General Psychiatry 26, 64-67 (1972).
29 Gallagher, S. Agency, ownership, and alien control in schizophrenia. Advances in Consciosuness 59, 89-104 (2004).
30 Lezak, M., Howieson, D. & Loring, D. Executive functions and motor performance. Neuropsychological assessment 3, 650-685 (1995).

31 Miller, T. J., McGlashan T.H., Woods S.W., Stein K., Driesen N., Corcoran C.M., Hoffman R., Davidson L.. Symptom assessment in schizophrenic prodromal states. Psychiatric Quarterly 70, 273-287 (1999).
32 Schultze-Lutter, F., Addington, J., Ruhrmann, S. & Klosterkötter, J. Schizophrenia proneness instrument, adult version (SPI-A). Rome: Giovanni Fioriti (2007).
33 Frith, C. The self in action: Lessons from delusions of control. Consciousness and Cognition 14, 752-770 (2005).

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Author contributions

A.S., F.B., P.P. designed the study, carried out the experiments, analysed data and wrote the paper, M.S. carried out the experiments and analysed data, M.H. and H.B designed and built the robotic device, P.P., K.D, J.P. and P.C. carried out clinical work, M.M., G.S., H.D. carried out the experiments, A.G. and R.S. analysed data, G.R. designed the study, built the robotic device, collected data, analysed data and wrote the paper; O.B. designed the study, analysed the data, and wrote the paper.

Declaration of Interests

The authors declare no competing interests.

Figures

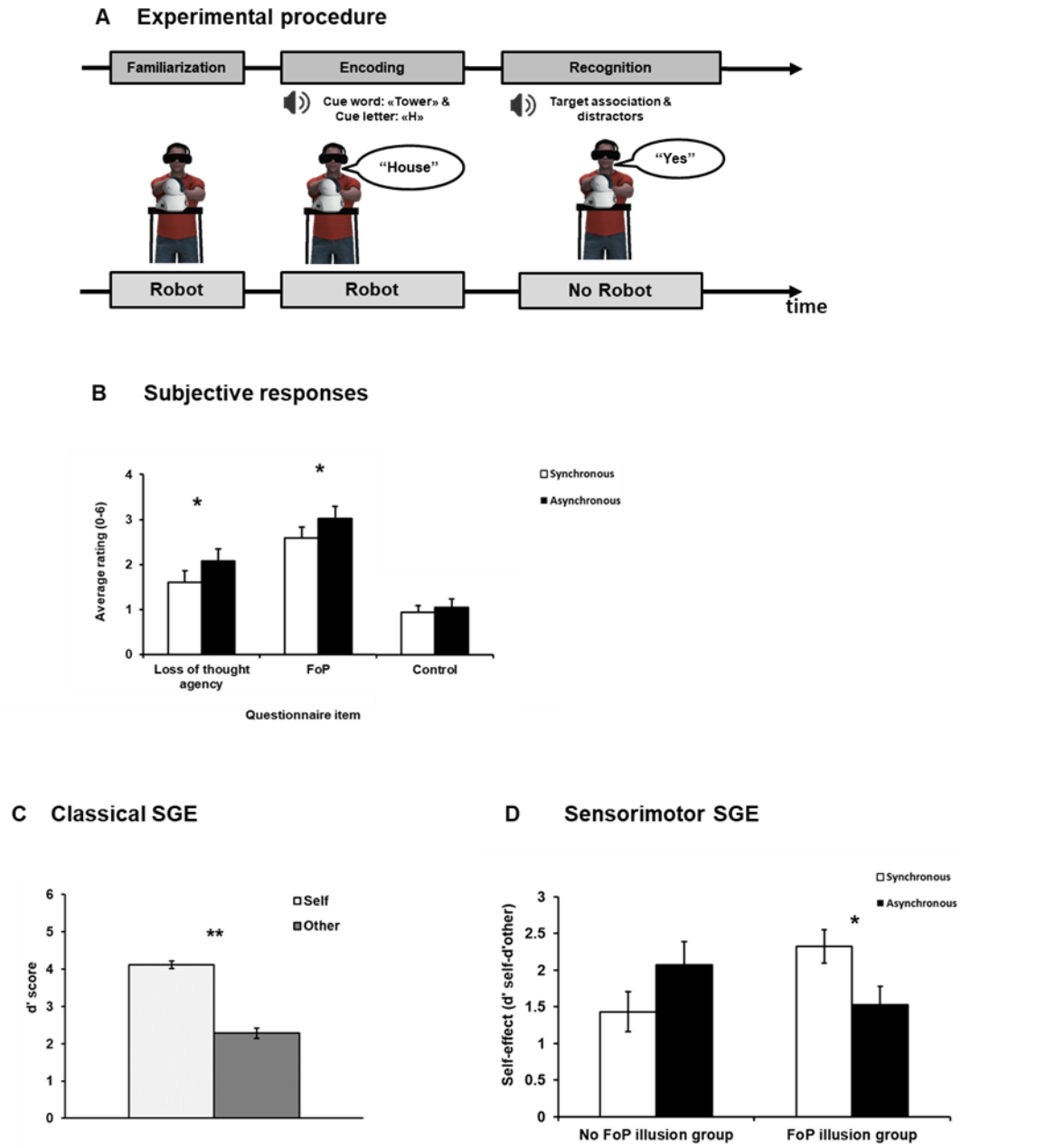


Figure 1. Thought generation (Experiment 1). (A) Experimental procedure for Experiment 1. During encoding, participants operate the robotic system in synchronous or asynchronous mode, followed by the memory recognition phase. Participants answered whether they had generated (active condition) or heard (passive condition) the word. (B) Classical SGE (d') was higher in the active versus passive conditions. (C) Only individuals experiencing the FoP had significantly less self-advantage (sensorimotor SGE; d'active–d'passive) in the asynchronous as compared to the synchronous condition (error bars standard error of mean). (D) Participants reported stronger FoP, passivity experiences, and loss of thought agency during the asynchronous versus synchronous condition.

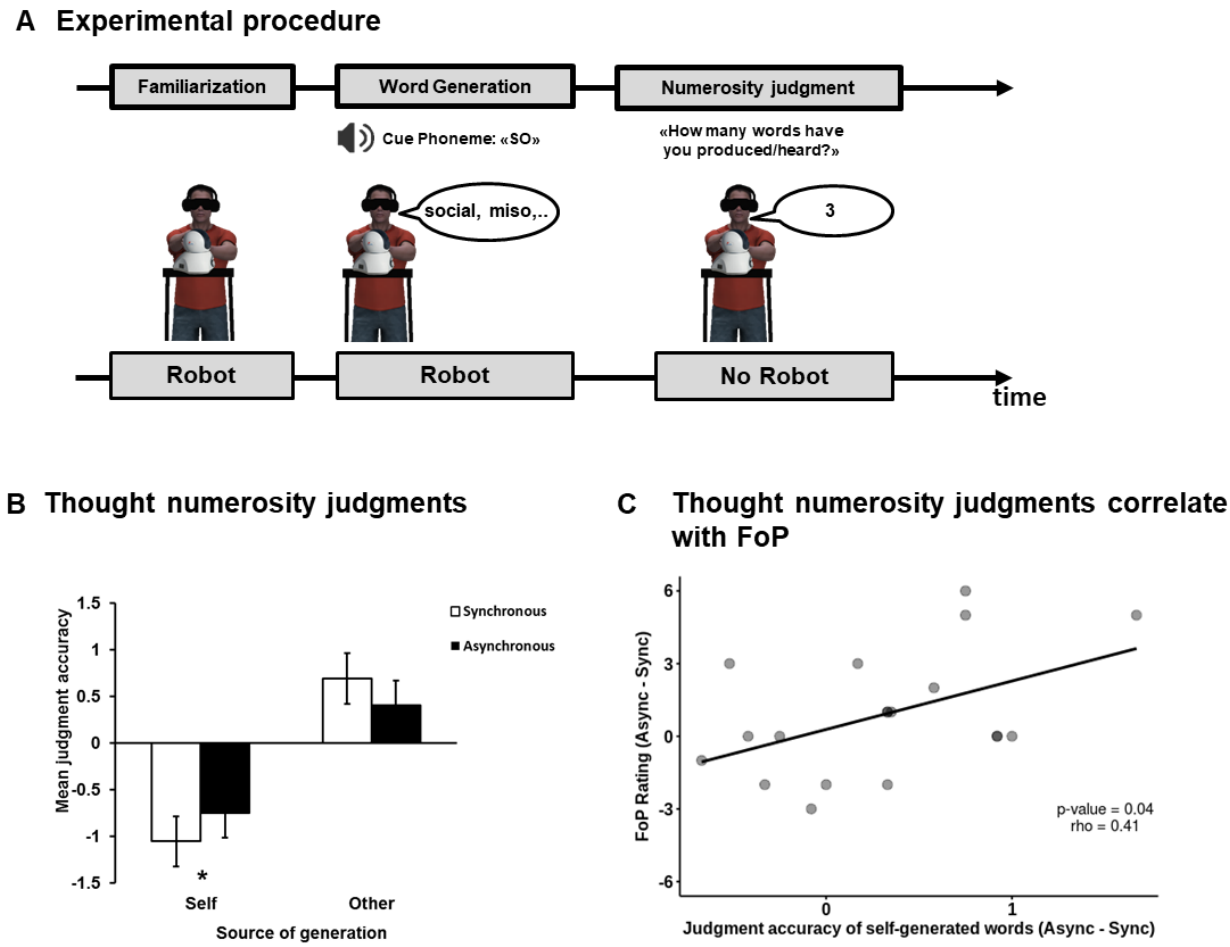
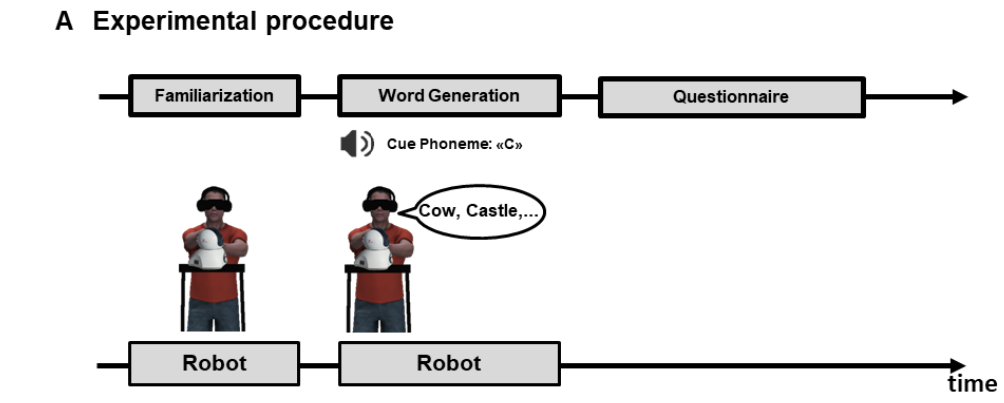
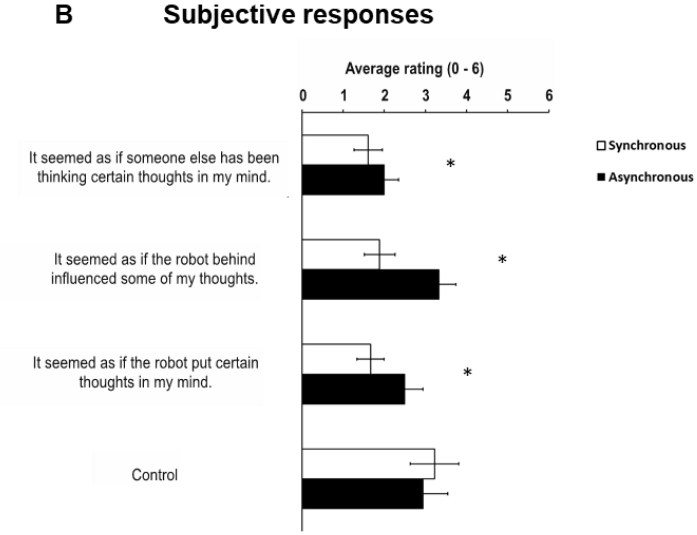


Figure 2. Thought numerosity task (Experiment 2). (A) While operating the robotic system in synchronous or asynchronous mode participants performed the thought numerosity task (either active, self-generating, or passive conditions) (Supplementary Information). (B) Thought numerosity judgments are shown. Participants showed a general suppression of numerosity judgments for self-generated words (active conditions). Crucially, this self-suppression was reduced during asynchronous versus synchronous condition. There was no such change for other-generated words (passive condition). (C) Correlation analysis shows a significant positive correlation between the magnitude of numerosity judgment suppression and the differential FoP score. Error bars show standard errors of the mean. * $p<0.05$, ** $p<0.01$.





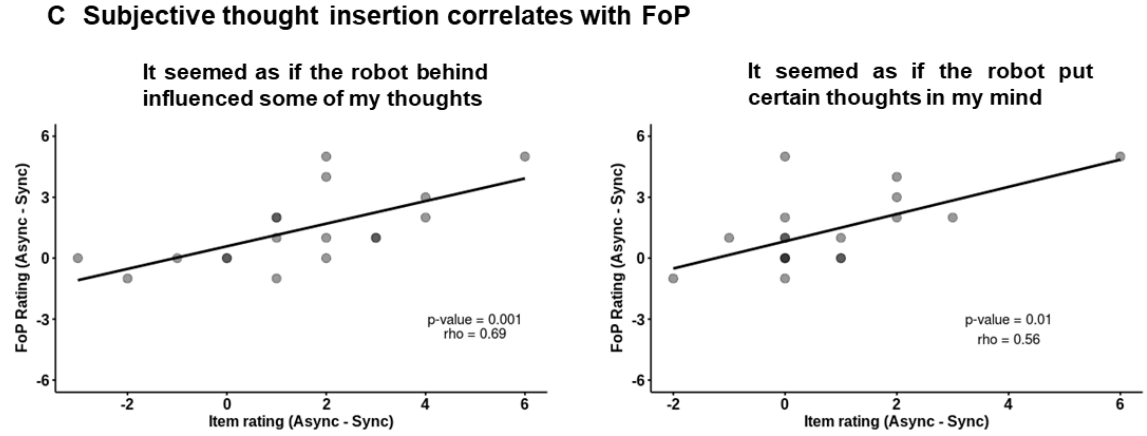


Figure 3. Thought Insertion (Experiment 3). (A) At the beginning of each condition, participants heard a phoneme and then had three minutes to generate as many words starting with the specified phoneme as they could (Supplementary Information). (B) Subjective responses show that during the FoP-inducing asynchronous condition, participants agreed more with statements about TI and influencing. (C) Correlation between FoP scores and thought- related experience ratings revealed a significant positive correlation between the differential FoP score and differential ratings of items reflecting TI and thought influencing.

Supplementary Information

Supplementary results

Experiment 1: Thought agency

FoP Questionnaire. Participants experienced stronger sensation to be touched by another person in the asynchronous condition (synchronous: M = 3.20, SD = 1.71; asynchronous: M = 3.84, SD= 1.78; Z = -2.399, p = 0.005) and also reported a stronger feeling of a presence in the same, asynchronous condition (synchronous: M = 2.80, SD = 1.55; asynchronous: M = 3.24, SD = 1.48; Z = -2.361, p = 0.005). Conversely, the participants reported stronger illusory self-touch when they operated the robotic system in the synchronous condition (synchronous: M = 3.18, SD = 1.50; asynchronous: M = 2.24, SD = 1.43; Z = -2.985, p = 0.002). The ratings of the control items were low and not significantly affected by the sensorimotor stimulation (M < 1.5, SD < 1.80, all p< 0.05), except the item: "I felt as if I was behind my body" (synchronous: M = 2.30, SD = 1.77; asynchronous: M = 1.82, SD = 1.47; Z = -2.623, p = 0.005).

Subjective loss of thought agency (Questionnaire). The effect of sensorimotor stimulation modulation was also observed for the sense of agency over self-generated thoughts. The participants reported a reduced sense of agency ("It seemed as if I was not the one who generated the words") for the words they generated in the asynchronous (M = 2.21, SD = 1.728) as compared to the synchronous condition (M = 1.73, SD = 1.625; Z = -1.894, p = 0.029). The sensorimotor stimulation did not modulate the experience of thought insertion proper (synchronous: M = 2.97, SD = 1.610, asynchronous: M = 3.03, SD = 1.794; Z = - .340, p = 0.367) or ownership for self-generated words (synchronous: M = 1.55, SD = 1.348, asynchronous: M = 1.67, SD = 1.407; Z = - 0.537, p = 0.296), although in both cases ratings were higher in the asynchronous condition.

Pilot Experiment: Verification of the generation effect with auditory stimuli. To confirm that the generation effect can be also achieved by using selected word stimuli presented in the auditory modality, prior to the main experiment we conducted a pilot experiment without the robotic sensorimotor stimulation. 6 native French speaking participants (3 females, M = 20.6 years, SD

= 2.7) were recruited to participate in this experiment. They completed two self-generated and two other-generated conditions in a randomized order. Two-tailed paired-sample t-test showed that the accuracy rate (t(5) = 5.289, p = 0.003), as well as sensitivity (t(5) = 7,264, p = 0.001), in the recognition task was significantly higher for the self-generated words, demonstrating that the generation effect was replicated with the selected auditory word material.

Behavioral paradigm: Self-generation effect. The analysis of performance in the memory task replicates the classical self-generation effect (SGE [5]), as the main effect of source was significant (self: M = 4.12, SD = 0.45; other: M = 2.28, SD = 0.65; F(1,20) = 180.86, p < 0.0001). Importantly, this self-effect was significantly modulated by the manipulation of the sensorimotor stimulation in relation to the experience of FoP (interaction between generation source, sensorimotor stimulation and covariate FoP score: (F(1,20) = 6.95, p = 0.016). To investigate this interaction, we split the sample into two groups according to the experience of FoP (No-FoP group: Fop score ≤ 0; FoP group: FoP score > 0) and tested whether the two groups differed in the modulation of the self-effect due to sensorimotor mismatch. The mixed ANOVA on the strength of the self-effect (calculated as d' for recognition of self-generated – d' for other generated words) showed a significant interaction between sensorimotor stimulation and group (F(1,20) = 7.217, p = 0.014). Post-hoc comparisons further showed a significant decrease of the self-effect in the asynchronous condition, but only in the group, which experienced the FoP (synchronous: M = 2.33, SD = 0.75; asynchronous: M = 1.53, SD = 0.83; one-tailed t-test: t(10) = 2.148, p = 0.029; No-FoP group: synchronous: M = 1.43; SD = 0.90; asynchronous: M = 2.07, SD = 1.04, one-tailed t-test: t(10) = 1.660, p = 0.064).

Experiment 2: Thought numerosity task (behavioral measure of thought insertion proper)

The number of generated words in the thought numerosity judgment. In Experiment 2 (Numerosity judgment), we used the same auditory verbal stimuli as in Experiment 1 (in total 420 French words and 22 phonemes). To verify that the found differences in numerosity judgment were not due to the differences in the number of generated words between the experimental conditions, we conducted a repeated-measures ANOVA with source and sensorimotor stimulation as within- subject factors. The analysis showed that the number of generated words did not differ between the active (M = 7.95, SD = 2.02) and passive conditions (M = 8.11, SD = 0.33; F(1,18) = 0.115, p

= 0.738), neither it was modulated by the sensorimotor stimulation (synchronous: M = 8.18, SD = 1.18; asynchronous: M = 7.88, SD = 0.89; F(1,18) = 3.079, p = 0.096) or the interaction between the source and sensorimotor stimulation (F(1,18) = 0.944, p = 0.344).

Absolute accuracy in the thought numerosity judgment. To verify whether the difference in the numerosity judgments was not due to differences in cognitive load between the active and passive conditions or between synchronous and asynchronous conditions, we analyzed the absolute accuracy. This was defined as a percentage of trials when the numerosity judgment was correct within each experimental condition. The repeated measures ANOVA showed that the absolute accuracy was not affected by the Source (F(1,18) = 0.833, p = 0.374), Sensorimotor stimulation (F(1,18) = 0.810, p = 0.380) or their interaction (F(1,18) = 1.118, p = 0.304).

Experiment 3: Thought Insertion

Analyses of the questionnaire data revealed that the synchrony between participants' movements and received tactile feedback significantly modulated ratings of the questionnaire items related to thought insertion and thought influencing. In particular, as compared to the synchronous, the asynchronous mode of stimulation resulted in significantly higher ratings of the items assessing thought insertion: "It seemed as if someone else has been thinking certain thoughts in my mind" (synchronous: M =1.61, SD = 1.38, asynchronous: M = 2.00, SD = 1.41; Z = 2.111, p = 0.03), thought influencing: "It seemed as if the robot behind influenced some of my thoughts" (synchronous: M = 1.89, SD = 1.49, asynchronous: M = 3.33, SD = 1.64; Z = 2.345, p = 0.01) and a significant higher ratings of the item assessing robotically-induced thought insertion: "It seemed as if the robot put certain thoughts in my mind" (synchronous: M = 1.67, SD = 1.33, asynchronous: M = 2.5, SD = 1.76; Z = 1.911, p = 0.03). The ratings of other questionnaire items were not significantly modulated by the sensorimotor mismatch (all p > 0.05). See Table S1.

Supplementary figures

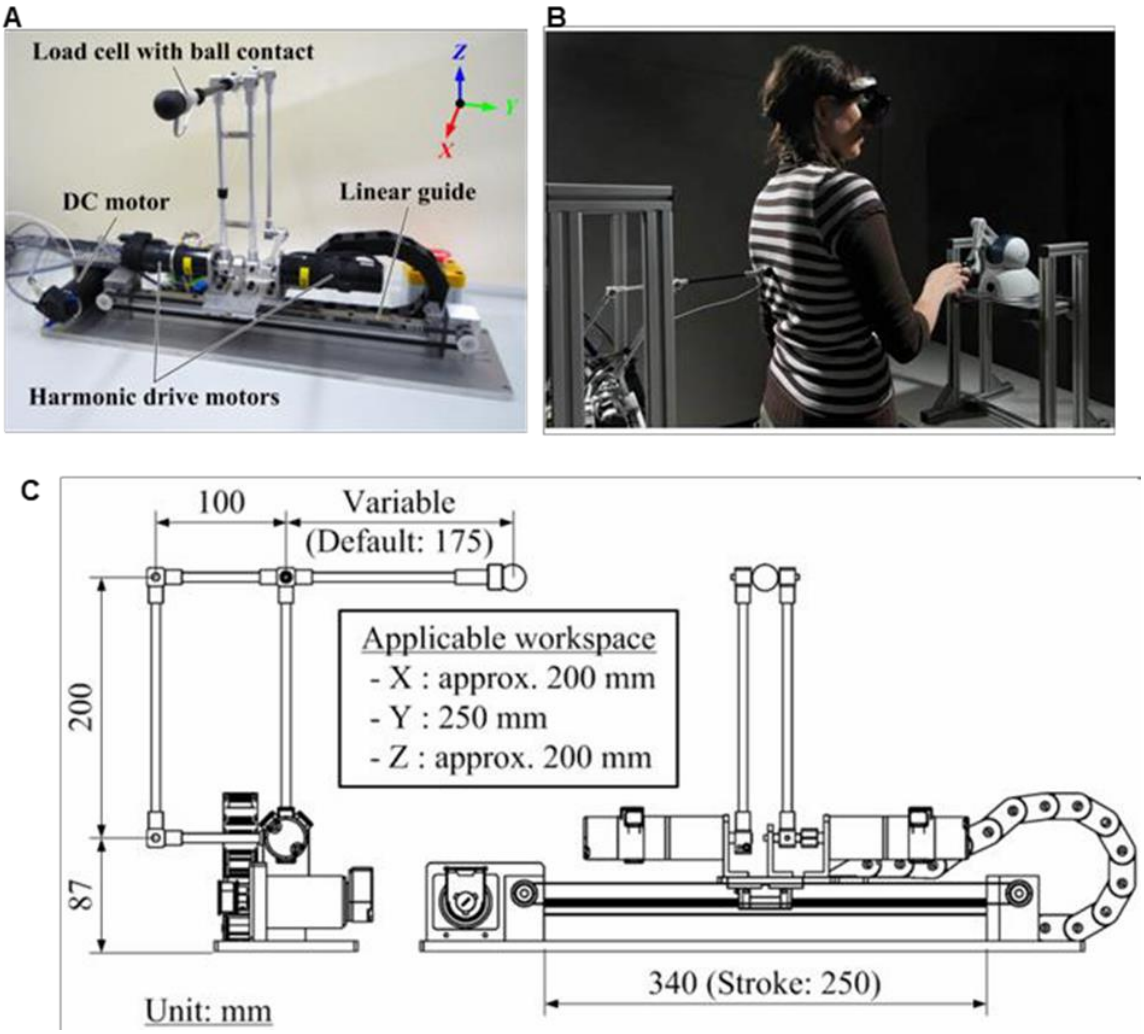


Figure S1. Lead-follow robotic system (Experiment 1-4). This system is composed of a commercial haptic interface, the lead robot (Phantom Omni, SensAble Technologies), and a three degree-of-freedom robot (follow robot). The follow device consists of two mechanisms: a belt- drive mechanism and a parallel-link mechanism. The belt-drive mechanism is made up of a belt linked to a direct-drive DC motor (RE 40, Maxon) moving a carrier on a linear guide allowing movements in the y (forward-backward) direction. The parallel-link mechanism is actuated through two harmonic drive motors (RH-8D 6006, Harmonic Drive Systems) and enables both tapping and stroking in x (right-left) and z (up-down) directions. These three motors equipped with optical encoders for positions sensing are connected to motor drivers (4-Q-DC Servoamplifier LSC 30/2 & ADS 50/5, Maxon) that receive the command voltages from a computer via PCI data acquisition cards (NI PCI-6221 & NI PCI-6014, National Instruments). The overall workspace of the follow device is 200mm in the x direction, 250mm in the y direction and 200mm in the z direction. A load cell (ELPFTIM-50N, Measurement Specialties) is attached on the tip of the follow device in order to measure contact force.

Questionnaire item	M		SEM		Z	p
	Sync	Async	Sync	Async		
Thought influencing						
It seemed as if the robot behind influenced some of my thoughts.	1.89	3.33	0.35	0.39	2.34	0.01
It seemed as if some outside force or person has influenced some of my thoughts.	2.28	3.00	0.36	0.36	1.25	0.12
Thought insertion						
It seemed as if someone else has been thinking certain thoughts in my mind.	1.61	2.00	0.32	0.33	2.11	0.03
It seemed as if the robot put certain thoughts in my mind.	1.67	2.50	0.31	0.41	1.91	0.03
It seemed as if some outside force or person has put certain thoughts into my mind.	2.44	2.44	0.34	0.42	0.36	0.38
It seemed as if some thoughts (that were not my own) intruded my mind.	2.28	2.06	0.40	0.38	0.21	0.45
Thought ownership						
It seemed as if certain thoughts I had belonged to someone else.	1.61	2.00	0.33	0.39	0.98	0.19
Thought withdrawal						
It seemed as if some of my thoughts have been removed from my mind.	4.00	4.39	0.40	0.26	0.80	0.23
Parasite thoughts						
It seemed as if the train of my thoughts have been interrupted by some unimportant "parasite" thoughts.	4.17	4.28	0.34	0.31	0.41	0.34
Thought echoing						
It seemed as if some of my thoughts were echoed back to me.	2.72	2.89	0.52	0.40	0.05	0.49
Voice distortion						
It seemed as if my voice became distorted.	2.33	2.61	0.59	0.54	0.88	0.21
It seemed as if my speech became hard to understand.	3.22	2.94	0.55	0.56	0.94	0.19

Table S2. Results from Experiment 3. All items from the Thought insertion questionnaire with average item ratings, standard errors of the mean for synchronous and asynchronous conditions, and Z and 2-tailed p-values of Wilcoxon signed rank tests for the differences between the ratings of synchronous and asynchronous conditions. TI related questions are: Q1, Q3, Q7, Q8, Q10 and Q11. Control Questions are: Q2, Q4, Q5, Q7, Q9, Q12.

BIBLIOGRAPHY

Aarsland, D., Larsen, J.P., Tandberg, E., Laake, K., 2000. Predictors of nursing home placement in Parkinson's disease: A population-based, prospective study. J. Am. Geriatr. Soc. 48, 938–942.

American Psychiatric Association, 2000. DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition TR.

Anobile, G., Cicchini, G.M., Burr, D.C., 2016. Number As a Primary Perceptual Attribute: A Review. Perception 45, 5–31.

Ardila, A., Gómez, J., 1988. Paroxysmal "Feeling of Somebody Being Nearby." Epilepsia 29, 188–189.

Arsalidou, M., Taylor, M.J., 2011. Is 2+2=4? Meta-analyses of brain areas needed for numbers and calculations. Neuroimage 54, 2382–2393.

Arzy, S., Seeck, M., Ortigue, S., Spinelli, L., Blanke, O., 2006. Induction of an illusory shadow person. Nature 443, 287.

Balleine, B.W., Delgado, M.R., Hikosaka, O., 2007. The role of the dorsal striatum in reward and decision-making. J. Neurosci. 27, 8161–8165.

Bansal, S., Ford, J.M., Spering, M., 2018. The function and failure of sensory predictions. Ann. N. Y. Acad. Sci. 1426, 199–220.

Benazet, M., Thénault, F., Whittingstall, K., Bernier, P.M., 2016. Attenuation of visual reafferent signals in the parietal cortex during voluntary movement. J. Neurophysiol. 116, 1831–1839.

Bernasconi, F., Blondiaux, E., Potheegadoo, J., Stripeikyte, G., Pagonabarraga, J., Bejr-Kasem, H., Bassolino, M., Akselrod, M., Martinez-Horta, S., Sampedro, F., Hara, M., Horvath, J., Franza, M., Konik, S., Bereau, M., Ghika, J.-A., Burkhard, P.R., Ville, D. Van De, Faivre, N., Rognini, G., Krack, P., Kulisevsky, J., Blanke, O., 2020. Sensorimotor hallucinations in Parkinson' s disease. bioRxiv.

Biswal, B., Zerrin Yetkin, F., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar mri. Magn. Reson. Med.

Biswal, B.B., 2012. Resting state fMRI: A personal history. Neuroimage.

Biswas, A.B., Furniss, F., 2016. Cognitive phenotype and psychiatric disorder in 22q11.2 deletion syndrome: A review. Res. Dev. Disabil. 53–54, 242–257.

Blakemore, S.-J., Wolpert, D.M., Frith, C.D., 2000. Why you can't tickle yourself. Neuroreport 11, 11–16.

Blakemore, S J, Smith, J., Steel, R., Johnstone, C.E., Frith, C.D., 2000. The perception of self-produced sensory stimuli in patients with auditory hallucinations and passivity experiences: evidence for a breakdown in self-monitoring. Psychol. Med. 30, 1131–9.

Blakemore, S.J., Wolpert, D.M., Frith, C.D., 1998. Central cancellation of self-produced tickle sensation. Nat. Neurosci. 1, 635–640.

Blanke, O., 2012. Multisensory brain mechanisms of bodily self-consciousness. Nat. Rev. Neurosci. 13, 556–571.

Blanke, O., Arzy, S., Landis, T., 2008. Illusory perceptions of the human body and self. Neuropsychology 88, 429–458.

Blanke, O., Ortigue, S., Coeytaux, A., Martory, M.-D., Landis, T., 2003. Hearing of a presence. Neurocase case Stud. Neuropsychol. neuropsychiatry, Behav. Neurol. 9, 329–339.

Blanke, O., Pozeg, P., Hara, M., Heydrich, L., Serino, A., Yamamoto, A., Higuchi, T., Salomon, R., Seeck, M., Landis, T., Arzy, S., Herbelin, B., Bleuler, H., Rognini, G., 2014b. Neurological and robot-controlled induction of an apparition. Curr. Biol. 24, 2681–2686.

Blanke, O., Slater, M., Serino, A., 2015. Behavioral, Neural, and Computational Principles of Bodily Self-Consciousness. Neuron 88, 145–166.

Blondiaux, E., Potheegadoo, J., Stripeikyte, G., Jenni, L., Maeder, J., Pouillard, V., Bernasconi, F., Sandini, C., Micol, E., Schneider, M., Eliez, S., Blanke, O., n.d. Individuals with the 22q11.2 deletion syndrome show lack of sensitivity to sensorimotor conflicts. *In preparation*.

Boes, A.D., Prasad, S., Liu, H., Liu, Q., Pascual-Leone, A., Caviness, V.S., Fox, M.D., 2015. Network localization of neurological symptoms from focal brain lesions. Brain 138, 3061–3075.

Brooks, J.X., Cullen, K.E., 2019. Predictive Sensing: The Role of Motor Signals in Sensory Processing. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 4, 842–850.

Brugger, P., 1994. Are “presences” preferentially felt along the left side of one’s body?

Brugger, P., Regard, M., Landis, T., 1996. Unilaterally Felt “Presences”: The Neuropsychiatry of One’s Invisible Doppelgänger. Neuropsychiatry. Neuropsychol. Behav. Neurol. 9, 114–122.

Brugger, P., Regard, M., Landis, T., Oelz, O., 1999. Hallucinatory experiences in extreme-altitude climbers. Neuropsychiatry. Neuropsychol. Behav. Neurol.

Burr, D.C., Anobile, G., Arrighi, R., 2018. Psychophysical evidence for the number sense. Philos. Trans. R. Soc. B Biol. Sci. 373.

Bychowski, G., 1943. Disorders of the body-image in the clinical pictures of psychoses. J Nerv Ment Dis 97.

Cho, R., Wu, W., 2013. Mechanisms of auditory verbal hallucination in schizophrenia. Front. Psychiatry 4, 1–8.

Critchley, M., 1979. The divine banquet of the brain.

Critchley, M., 1955. The idea of a presence. Acta Psychiatr. Scand. 30, 155–168.

Critchley, M., 1950. The body-image in neurology. Lancet 1, 335–340.

Crossley, N. a., Mechelli, A., Fusar-Poli, P., Broome, M.R., Matthiasson, P., Johns, L.C., Bramon, E., Valmaggia, L., Williams, S.C.R., McGuire, P.K., 2009. Superior temporal lobe dysfunction and frontotemporal dysconnectivity in subjects at risk of psychosis and in first-episode psychosis. Hum. Brain Mapp. 30, 4129–4137.

Dacquino, C., De Rossi, P., Spalletta, G., 2015. Schizophrenia and bipolar disorder: The road from similarities and clinical heterogeneity to neurobiological types. Clin. Chim. Acta.

Dehaene, S., 1997. The Number Sense. Oxford Univ. Press.

Deiber, M.P., Honda, M., Ibañez, V., Sadato, N., Hallett, M., 1999. Mesial motor areas in self-initiated versus externally triggered movements examined with fMRI: Effect of movement type and rate. J. Neurophysiol. 81, 3065–3077.

Engerth, G., Hoff, H., 1929. Ein Fall von Halluzinationen im hemianoptischen Gesichtsfeld. Beitrag zur Genese der optischen Halluzinationen. Monatsschr Psychiatr Neurol 74, 246–256.

Farrer, C., Frith, C.D., 2002. Experiencing oneself vs another person as being the cause of an action: The neural correlates of the experience of agency. Neuroimage 15, 596–603.

Fénelon, G., Alves, G., 2010. Epidemiology of psychosis in Parkinson’s disease. J. Neurol. Sci. 289, 12–17.

Fénelon, G., Mahieux, F., Huon, R., Ziégler, M., 2000. Hallucinations in Parkinson’s disease: prevalence, phenomenology and risk factors. Brain 123, 733–745.

Ffytche, D.H., Pereira, J., Ballard, C., Chaudhuri, K.R., Weintraub, D., Aarsland, D., 2017. Risk factors for early psychosis in PD: insights from the Parkinson's Progression Markers Initiative. J. Neurol. Neurosurg. Psychiatry 88, 325–331.

Fletcher, P.C., Frith, C.D., 2009. Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. Nat. Rev. Neurosci. 10, 48–58.

Ford, J.M., Palzes, V.A., Roach, B.J., Mathalon, D.H., 2014. Did I Do That? Abnormal Predictive Processes in Schizophrenia When Button Pressing to Deliver a Tone. Schizophr. Bull. 40, 804–812.

Frisina, P.G., Borod, J.C., Foldi, N.S., Tenenbaum, H.R., 2008. Depression in Parkinson's disease: Health risks, etiology, and treatment options. Neuropsychiatr. Dis. Treat. 4, 81–91.

Friston, K., Brown, H.R., Siemerkus, J., Stephan, K.E., 2016. The dysconnection hypothesis (2016). Schizophr. Res. 176, 83–94.

Friston, K.J., 1998. The disconnection hypothesis. Schizophr. Res. 30, 115–25.

Friston, K.J., Frith, C.D., 1995. Schizophrenia: a disconnection syndrome? Clin. Neurosci.

Friston, K.J., Frith, C.D., Turner, R., Frackowiak, R.S.J., 1995. Characterizing evoked hemodynamics with fMRI. Neuroimage.

Friston, K.J., Harrison, L., Penny, W., 2003. Dynamic causal modelling. Neuroimage 19, 1273–1302.

Friston, K.J., Preller, K.H., Mathys, C., Cagnan, H., Heinzle, J., Razi, A., Zeidman, P., 2019. Dynamic causal modelling revisited. Neuroimage 199, 730–744.

Frith, C., 2012. Explaining delusions of control: The comparator model 20years on. Conscious. Cogn. 21, 52–54.

Frith, C., 2005. The Self in Action: Lessons From Delusions of Control. Conscious. Cogn. 14, 752–770.

Frith, C.D., 1992. The cognitive neuropsychology of schizophrenia. Hove, U.K.: Lawrance Erlbaum.

Frith, Chris D., Blakemore, S.J., Wolpert, D.M., 2000. Explaining the symptoms of schizophrenia: Abnormalities in the awareness of action. Brain Res. Rev. 31, 357–363.

Gallagher, S., 2004. Neurocognitive models of schizophrenia: A neurophenomenological critique. Psychopathology 37, 8–19.

Gallagher, S., 2000. Philosophical conceptions of the self: Implications for cognitive science. Trends Cogn. Sci. 4, 14–21.

Glover, G.H., 2011. Overview of functional magnetic resonance imaging. Neurosurg. Clin. N. Am. 22, 133–139.

González-Vivas, C., Soldevila-Matías, P., Sparano, O., García-Martí, G., Martí-Bonmatí, L., Crespo-Facorro, B., Aleman, A., Sanjuan, J., 2019. Longitudinal studies of functional magnetic resonance imaging in first-episode psychosis: A systematic review. Eur. Psychiatry 59, 60–69.

Graham-Schmidt, K.T., Martin-Iverson, M.T., Waters, F.A.V., 2018. Self- and other-agency in people with passivity (first rank) symptoms in schizophrenia. Schizophr. Res. 192, 75–81.

Haggard, P., 2017. Sense of agency in the human brain. Nat. Rev. Neurosci. 18, 197–208.

Haggard, P., Whitford, B., 2004. Supplementary motor area provides an efferent signal for sensory suppression. Cogn. Brain Res. 19, 52–58.

Hahamy, A., Calhoun, V., Pearlson, G., Harel, M., Stern, N., Attar, F., Malach, R., Salomon, R., 2014. Save the Global: Global Signal Connectivity as a Tool for Studying Clinical Populations with Functional Magnetic Resonance Imaging. Brain Connect. 4, 395–403.

Hara, M., Salomon, R., van der Zwaag, W., Kober, T., Rognini, G., Nabae, H., Yamamoto, A., Blanke,

O., Higuchi, T., 2014. A novel manipulation method of human body ownership using an fMRI-compatible master-slave system. J. Neurosci. Methods 235, 25–34.

Hécaen, H., Ajuriaguerra, J., 1952. Meconnaissances et Hallucinations Corporelles: Intégration et Désintégration de la Somatognosie. Masson (in French).

Holroyd, S., Currie, L., Wooten, G.F., 2001. Prospective study of hallucinations and delusions in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 70, 734–738.

Hughes, G., Waszak, F., 2011. ERP correlates of action effect prediction and visual sensory attenuation in voluntary action. Neuroimage 56, 1632–1640.

Jack, B.N., Le Pelley, M.E., Han, N., Harris, A.W.F., Spencer, K.M., Whitford, T.J., 2019. Inner speech is accompanied by a temporally-precise and content-specific corollary discharge. Neuroimage 198, 170–180.

Jaspers, K., 1913. Über leibhaftige Bewusstheiten (Bewusstheitstaüschungen), ein psychopathologisches Elementarsymptom. Zeitschrift für Pathopsychologie 2, 150–161.

Jeannerod, M., 2003. The mechanism of self-recognition in humans. Behav. Brain Res. 142, 1–15.

Jo, H.G., Habel, U., Schmidt, S., 2019. Role of the supplementary motor area in auditory sensory attenuation. Brain Struct. Funct. 224, 2577–2586.

Karbasforoushan, H., Woodward, N.D., 2013. Resting-State Networks in Schizophrenia. Curr. Top. Med. Chem. 12, 2404–2414.

Kendler, K.S., Mishara, A., 2019. The Prehistory of Schneider's First-Rank Symptoms: Texts from 1810 to 1932. Schizophr. Bull. 45, 971–990. https://doi.org/10.1093/schbul/sbz047

Kilteni, K., Andersson, B.J., Houborg, C., Ehrsson, H.H., 2018. Motor imagery involves predicting the sensory consequences of the imagined movement. Nat. Commun. 9, 1–9.

Kilteni, K., Ehrsson, H.H., 2019. Functional connectivity between the cerebellum and somatosensory areas implements the attenuation of self-generated touch. J. Neurosci. 1732–19.

Kim, B.S., Im, H.I., 2019. The role of the dorsal striatum in choice impulsivity. Ann. N. Y. Acad. Sci. 1451, 92–111.

Koehler, K., 1979. First rank symptoms of schizophrenia: Questions concerning clinical boundaries. Br. J. Psychiatry 134, 236–248.

Lau, H.C., Rogers, R.D., Haggard, P., Passingham, R.E., 2004. Attention to Intention. Science (80-.). 303, 1208–1210.

Lawrie, S.M., Buechel, C., Whalley, H.C., Frith, C.D., Friston, K.J., Johnstone, E.C., 2002. Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations. Biol. Psychiatry 51, 1008–1011.

Lhermitte, J., 1939. L'image de notre corps, Paris: Edi. ed.

Lichtenstein, P., Yip, B.H., Björk, C., Pawitan, Y., Cannon, T.D., Sullivan, P.F., Hultman, C.M., 2009. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 373, 234–239.

Liu, X., Zhang, N., Chang, C., Duyn, J.H., 2018. Co-activation patterns in resting-state fMRI signals. Neuroimage 1–10.

Llorca, P.M., Pereira, B., Jardri, R., Chereau-Boudet, I., Brousse, G., Misdrahi, D., Fénelon, G., Tronche, A.-M., Schwan, R., Lançon, C., Marques, A., Ulla, M., Derost, P., Debilly, B., Durif, F., de Chazeron, I., 2016. Hallucinations in schizophrenia and Parkinson's disease: an analysis of sensory modalities involved and the repercussion on patients. Sci. Rep. 6, 38152.

Martin, A.K., Gibson, E.C., Mowry, B., Robinson, G.A., 2016. Verbal Initiation, Suppression, and Strategy Use and the Relationship with Clinical Symptoms in Schizophrenia. J. Int. Neuropsychol. Soc. 22, 735–743.

Martin, J.R., Pacherie, E., 2013. Out of nowhere: Thought insertion, ownership and context-integration. Conscious. Cogn. 22, 111–122.

McDonald-McGinn, D.M., Sullivan, K.E., Marino, B., Philip, N., Swillen, A., Vorstman, J.A.S., Zackai, E.H., Emanuel, B.S., Vermeesch, J.R., Morrow, B.E., Scambler, P.J., Bassett, A.S., 2015. 22q11.2 deletion syndrome. Nat Rev Dis Prim. 1, 1–19.

McKeith, I.G., et al., 2017. Diagnosis and management of dementia with Lewy bodies. Neurology.

Mellor, C.S., 1970. First rank symptoms of schizophrenia. I. The frequnncy in schizophrenics on admission to hospital. II. Differences between individual first rank symptoms. Br. J. Psychiatry.

Mesholam-Gately, R.I., Giuliano, A.J., Goff, K.P., Faraone, S. V., Seidman, L.J., 2009. Neurocognition in First-Episode Schizophrenia: A Meta-Analytic Review. Neuropsychology 23, 315–336.

Miall, R.C., Wolpert, D.M., 1996. Forward models for physiological motor control. Neural Networks.

Mullins, S., Spence, S. a, 2014. Re-examining thought insertion : Semi-structured literature review and conceptual analysis. Br. J. Psychiatry 182, 293–298.

Murphy, K.C., Jones, L.A., Owen, M.J., 1999. High rates of schizophrenia in adults with velo-cardio-facial syndrome. Arch. Gen. Psychiatry 56, 940–945.

Mwansisya, T.E., Hu, A., Li, Y., Chen, X., Wu, G., Huang, X., Lv, D., Li, Z., Liu, C., Xue, Z., Feng, J., Liu, Z., 2017. Task and resting-state fMRI studies in first-episode schizophrenia: A systematic review. Schizophr. Res. 189, 9–18.

Nagahama, Y., Okina, T., Suzuki, N., Matsuda, M., 2010. Neural correlates of psychotic symptoms in dementia with Lewy bodies. Brain 133, 557–567.

Nicastro, N., Eger, A.F., Assal, F., Garibotto, V., 2018. Feeling of presence in dementia with Lewy bodies is related to reduced left frontoparietal metabolism. Brain Imaging Behav.

Nieder, A., 2018. Evolution of cognitive and neural solutions enabling numerosity judgements: Lessons from primates and corvids. Philos. Trans. R. Soc. B Biol. Sci. 373.

Nightingale, S., 1982. Somatoparaphrenia: A Case Report. Cortex 18, 463–467.

Oertel-Knöchel, V., Knöchel, C., Matura, S., Stäblein, M., Prvulovic, D., Maurer, K., Linden, D.E.J., van de Ven, V., 2014. Association between symptoms of psychosis and reduced functional connectivity of auditory cortex. Schizophr. Res. 160, 35–42.

Orepic, P., Rognini, G., Kannape, O.A., Faivre, N., 2020. Sensorimotor conflicts induce somatic passivity and louden quiet voices in healthy listeners. Biorxv 41, 1–32.

Pagonabarraga, J., Martinez-Horta, S., Fernández de Bobadilla, R., Pérez, J., Ribosa-Nogué, R., Marín, J., Pascual-Sedano, B., García, C., Gironell, A., Kulisevsky, J., 2016. Minor hallucinations occur in drug-naive Parkinson's disease patients, even from the premotor phase. Mov. Disord. 31, 45–52.

Piazza, M., Izard, V., Pinel, P., Le Bihan, D., Dehaene, S., 2004. Tuning curves for approximate numerosity in the human intraparietal sulcus. Neuron 44, 547–555.

Piazza, M., Mechelli, A., Price, C.J., Butterworth, B., 2006. Exact and approximate judgements of visual and auditory numerosity: An fMRI study. Brain Res. 1106, 177–188.

Pynn, L.K., DeSouza, J.F.X., 2013. The function of efference copy signals: Implications for

symptoms of schizophrenia. Vision Res. 76, 124–133.
Ravina, B., Marder, K., Fernandez, H.H., Friedman, J.H., McDonald, W., Murphy, D., Aarsland, D., Babcock, D., Cummings, J., Endicott, J., Factor, S., Galpern, W., Lees, A., Marsh, L., Stacy, M., Gwinn-Hardy, K., Voon, V., Goetz, C., 2007. Diagnostic criteria for psychosis in Parkinson's disease: Report of an NINDS, NIMH Work Group. Mov. Disord. 22, 1061–1068.
Rizzolatti, G., Ferrari, P.F., Rozzi, S., Fogassi, L., 2008. The inferior parietal lobule: Where action becomes perception, in: Percept, Decision, Action: Bridging the Gaps. pp. 129–145.
Rohde, M., Scheller, M., Ernst, M.O., 2014. Effects can precede their cause in the sense of agency. Neuropsychologia 65, 191–196.
Salomon, R., Progin, P., Griffa, A., Rognini, G., Do, K.Q., Conus, P., Marchesotti, S., Bernasconi, F., Hagmann, P., Serino, A., Blanke, O., 2020. Sensorimotor Induction of Auditory Misattribution in Early Psychosis. Schizophr. Bull. 1–8.
Satterthwaite, T.D., Baker, J.T., 2015. How can studies of resting-state functional connectivity help us understand psychosis as a disorder of brain development? Curr. Opin. Neurobiol. 30, 85–91.
Schneider, K., 1959. Clinical psychopathology. Grune & Stratton.
Schneider, K., 1957. [Primary & secondary symptoms in schizophrenia]. Fortschr. Neurol. Psychiatr. Grenzgeb. 25, 487–490.
Schneider, M., Schaer, M., Mutlu, A.K., Menghetti, S., Glaser, B., Debbané, M., Eliez, S., 2014. Clinical and cognitive risk factors for psychotic symptoms in 22q11.2 deletion syndrome: A transversal and longitudinal approach. Eur. Child Adolesc. Psychiatry 23, 425–436.
Serino, A., Pozeg, P., Bernasconi, F., Solcà, M., Hara, M., Progin, P., Stripeikyte, G., Dhanis, H., Salomon, R., Bleuler, H., Rognini, G., Blanke, O., n.d. Thought consciousness and source monitoring depend on robotically-controlled sensorimotor conflicts and illusory states. *In revision* iScience
Shergill, S.S., Samson, G., Bays, P.M., Frith, C.D., Wolpert, D.M., 2005. Evidence for sensory prediction deficits in schizophrenia. Am. J. Psychiatry 162, 2384–2386.
Shergill, S.S., White, T.P., Joyce, D.W., Bays, P.M., Wolpert, D.M., Frith, C.D., 2014. Functional magnetic resonance imaging of impaired sensory prediction in schizophrenia. JAMA Psychiatry 71, 28–35.
Shergill, S.S., White, T.P., Joyce, D.W., Bays, P.M., Wolpert, D.M., Frith, C.D., 2013. Modulation of somatosensory processing by action. Neuroimage 70, 356–362.
Skudlarski, P., Jagannathan, K., Anderson, K., Stevens, M.C., Calhoun, V.D., Skudlarska, B.A., Pearlson, G., 2010. Brain Connectivity Is Not Only Lower but Different in Schizophrenia: A Combined Anatomical and Functional Approach. Biol. Psychiatry 68, 61–69.
Sousa, P., Swiney, L., 2013. Thought insertion: Abnormal sense of thought agency or thought endorsement? Phenomenol. Cogn. Sci. 12, 637–654.
Stephan, K.E., Friston, K.J., Frith, C.D., 2009. Dysconnection in Schizophrenia: From Abnormal Synaptic Plasticity to Failures of Self-monitoring. Schizophr. Bull. 35, 509–527.
Stripeikyte, G., Pereira, M., Rognini, G., Potheegadoo, J., Faivre, N., Blanke, O. Cognitive self-attenuation during word numerosity estimations. *In preparation*.
Stripeikyte, G., Potheegadoo, J., Progin, P., Blondiaux, E., Do, K.Q., Conus, P., Hagmann, P., Faivre, N., Blanke, O. Fronto-temporal functional disconnection within the presence hallucination network in psychotic patients with passivity experiences. *Submitted* to Schz Bull.

Stripeikyte, G., Progin, P., Potheegadoo, J., Pozeg, P., Do, K.Q., Conus, P., Hagmann, P., Blanke, O.The cognitive and sensorimotor mechanisms of thought insertion. *In preparation*

Subramanian, D., Alers, A., Sommer, M.A., 2019. Corollary Discharge for Action and Cognition. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 4, 782–790.

Suedfeld, P., Mocellin, J.S.P., 1987. The "Sensed Presence" in Unusual Environments. Environ. Behav. 19, 33–52.

Taylor, M.A., 1972. Schneiderian First-Rank Symptoms and Clinical Prognostic Features in Schizophrenia. Arch. Gen. Psychiatry 26, 64–67.

Tian, X., Poeppel, D., 2010. Mental imagery of speech and movement implicates the dynamics of internal forward models. Front. Psychol. 1, 1–23.

Timm, J., SanMiguel, I., Keil, J., Schröger, E., Schönwiesner, M., 2014. Motor Intention Determines Sensory Attenuation of Brain Responses to Self-initiated Sounds. J. Cogn. Neurosci. 26, 1481–1489.

Tzeng, R.C., Tsai, C.F., Wang, C.T., Wang, T.Y., Chiu, P.Y., 2018. Delusions in Patients with Dementia with Lewy Bodies and the Associated Factors. Behav. Neurol. 2018, 6707291.

Viallon, M., Cuvinciuc, V., Delattre, B., Merlini, L., Barnaure-Nachbar, I., Toso-Patel, S., Becker, M., Lovblad, K.O., Haller, S., 2015. State-of-the-art MRI techniques in neuroradiology: principles, pitfalls, and clinical applications. Neuroradiology.

Walsh, A., Yun, I., 2013. Schizophrenia: Causes, crime, and implications for criminology and criminal justice. Int. J. Law, Crime Justice 41, 188–202.

Weiskrantz, L., Elliott, J., Darlington, C., 1971. Preliminary observations on tickling oneself. Nature 230, 598–599.

Whitford, T.J., 2019. Speaking-Induced Suppression of the Auditory Cortex in Humans and Its Relevance to Schizophrenia. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 4, 791–804.

Whitford, T.J., Jack, B.N., Pearson, D., Griffiths, O., Luque, D., Harris, A.W.F., Spencer, K.M., Le Pelley, M.E., 2017. Neurophysiological evidence of efference copies to inner speech. Elife 6, 1–23.

Whitten, L.A., 2012. Functional Magnetic Resonance Imaging (fMRI): An Invaluable Tool in Translational Neuroscience. RTI Press Publ. No. OP-0010-1212.

Williams, D.R., Warren, J.D., Lees, A.J., 2008. Using the presence of visual hallucinations to differentiate Parkinson's disease from atypical parkinsonism. J. Neurol. Neurosurg. Psychiatry 79, 652–655.

Wolpert, D.M., Flanagan, J.R., 2001. Motor prediction. Curr. Biol. 11, 729–732.

Wood, R.A., Hopkins, S.A., Moodley, K.K., Chan, D., 2015. Fifty percent prevalence of extracampine hallucinations in Parkinson's disease patients. Front. Neurol. 6, 1–9.

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Computer skills

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CAREER

Sep 2016 - Dec 2020 PhD student-assistant
Swiss Federal Institute of Technology (EPFL), Switzerland
Clinical functional (fMRI, PET), structural imaging (DSI), and behavioural data analysis, interpretation; experimental study design and execution; scientific communication and writing; teaching.

Jan 2016 - Jul 2016 Intern
University Psychiatry Clinics (UPK) Basel, Switzerland
Clinical fMRI data analysis.

Dec 2014 - Oct 2015 Intern
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Clinical structural MRI data analysis.

Nov 2013 - Jun 2014 Assistant
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EDUCATION

2016 - 2020 PhD in Neuroscience
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2014 - 2016 MSc in Neuroscience and Cognition, experimental and clinical track
Utrecht University, The Netherlands

2012 - 2013 Exchange student via ERASMUS program
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PUBLICATIONS

Submitted

- Fronto-temporal disconnection within the presence hallucination network in psychotic patients with passivity experiences. **Stripeikyte** et al. *submitted in Schz Bull.*
- Sensorimotor hallucinations in Parkinson's disease. Bernasconi*, Blondiaux*, Potheegadoo, **Stripeikyte**, et. al. BioRxiv: doi.org/10.1101/2020.05.11.054619
- Thought consciousness and source monitoring depend on robotically-controlled sensorimotor conflicts and illusory states. Serino, Pozeg, Bernasconi, Solcà, Hara, Progin, **Stripeikyte** et al.

In preparation

- Cognitive self attenuation during word numerosity estimations. **Stripeikyte** et al.
- The cognitive and sensorimotor brain mechanisms of thought insertion. **Stripeikyte** et al.
- PH-network alterations in Dementia with Lewy Bodies. Nicastro*, **Stripeikyte*** et al.
- Individuals with the 22q11.2 deletion syndrome show lack of sensitivity to sensorimotor conflicts. Blondiaux, Potheegadoo, **Stripeikyte** et al.